



# STIC Search Report

EIC 1700

STIC Database Tracking Number: 178934

**TO:** Ben Sackey  
**Location:** REM 5C18  
**Art Unit :** 1626  
**February 10, 2006**

**Case Serial Number:** 10/697545

**From:** Kathleen Fuller  
**Location:** EIC 1700  
**REMSEN 4B28**  
**Phone:** 571/272-2505  
**Kathleen.Fuller@uspto.gov**

## Search Notes

FOR OFFICIAL USE ONLY

*Mrs. Fuller*

Scientific and Technical Information Center

## SEARCH REQUEST FORM

Requester's Full Name: BEN SACKER Examiner #: 73489 Date: 2/17/06  
 Art Unit: 1626 Phone Number: 2-0704 Serial Number: 10/697545  
 Location, Bldg/Room#: 16M5B31 (Mailbox #): 5C18 Results Format Preferred (circle):  PAPER  DISK

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: isoxazoline deriv. as inhibitors of Matrix Metalloproteinase  
 Inventors (please provide full names): C. Xue et al.

SCIENTIFIC REFERENCE  
Sci & Tech Inf. Ctr

Earliest Priority Date:

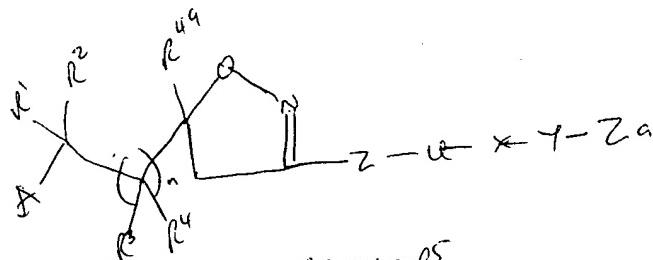
FEB 8 REC

## Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

Pat. &amp; T.M. Office

\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

 $R^1 \& R^2$  are as defined $R^3 \& R^4$  are alkylene.

A is  $-C(O)NHCO-$ , CONHOR<sup>5</sup>,

U is absent or C<sub>1-10</sub> alkylene

X is absent or C<sub>1-10</sub> alkylene

Y is O

Z is C<sub>3-13</sub> carbocycle substituted with 1-5 R<sup>b</sup>

Z<sup>a</sup> is C<sub>3-13</sub> carbocycle substituted with 1-5 R<sup>b</sup> consisting of N, O, and S(=O)<sub>2</sub>

Z<sup>c</sup> is 5-14 membered heterocycle consisting of N, O, and S(=O)<sub>2</sub> and substituted with 1-5 R<sup>c</sup>.

*Thanks*

## STAFF USE ONLY

Searcher: J. Fuller

Searcher Phone #: \_\_\_\_\_

Searcher Location: \_\_\_\_\_

Date Searcher Printed On: \_\_\_\_\_

Date Completed: 2/10/06Searcher Prep & Review Time: 30Online Time: 24

## Type of Search

NA Sequence (#)

AA Sequence (#)

Structure (#)

Bibliographic

Litigation

Fulltext

Other

## Vendors and cost where applicable

 STN Dialog Questel/Orbit Lexis/Nexis Westlaw WWW/Internet

In-house sequence systems

 Commercial Interference Oligomer Score/Length SPDI Endo/Trans

Other (specify)

SACKEY 10/697545 02/10/2006

Page 1

=> FILE REG

FILE 'REGISTRY' ENTERED AT 14:40:50 ON 10 FEB 2006  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2006 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file  
provided by InfoChem.

STRUCTURE FILE UPDATES: 8 FEB 2006 HIGHEST RN 873837-20-8  
DICTIONARY FILE UPDATES: 8 FEB 2006 HIGHEST RN 873837-20-8

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

\*\*\*\*\*  
\*  
\* The CA roles and document type information have been removed from \*  
\* the IDE default display format and the ED field has been added, \*  
\* effective March 20, 2005. A new display format, IDERL, is now \*  
\* available and contains the CA role and document type information. \*  
\*  
\*\*\*\*\*

Structure search iteration limits have been increased. See HELP SLIMITS  
for details.

REGISTRY includes numerically searchable data for experimental and  
predicted properties as well as tags indicating availability of  
experimental property data in the original document. For information  
on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

=> FILE HCPL )

FILE 'HCAPLUS' ENTERED AT 14:40:54 ON 10 FEB 2006  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is  
held by the publishers listed in the PUBLISHER (PB) field (available  
for records published or updated in Chemical Abstracts after December  
26, 1996), unless otherwise indicated in the original publications.  
The CA Lexicon is the copyrighted intellectual property of the  
the American Chemical Society and is provided to assist you in searching  
databases on STN. Any dissemination, distribution, copying, or storing  
of this information, without the prior written consent of CAS, is  
strictly prohibited.

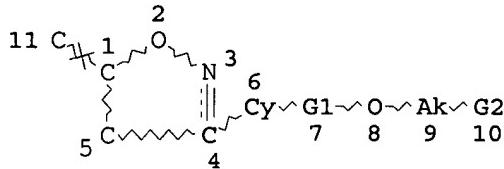
FILE COVERS 1907 - 10 Feb 2006 VOL 144 ISS 8  
FILE LAST UPDATED: 9 Feb 2006 (20060209/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

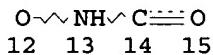
This file contains CAS Registry Numbers for easy and accurate substance identification.

=> D QUE

L4 STR



54 structures from claim 1  
Query



REP G1=(0-20) A

VAR G2=H/CY

NODE ATTRIBUTES:

NSPEC IS RC AT 11

CONNECT IS E3 RC AT 14

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE

L6 54 SEA FILE=REGISTRY SSS FUL L4

L7 6 SEA FILE=HCAPLUS ABB=ON L6

6 CA references

=> D L7 1-6 BIB ABS IND HITSTR

L7 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2004:430688 HCAPLUS

DN 141:7120

TI Preparation of isoxazoline derivatives as inhibitors of matrix metalloproteinases and/or TNF- $\alpha$  converting enzyme

IN Xue, Chu-Biao; Maduskuie, Thomas P.; Mercer, Stephen E.

PA Bristol-Myers Squibb Company, USA

SO PCT Int. Appl., 106 pp.

applicants

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004043349	A2	20040527	WO 2003-US34391	20031030
	WO 2004043349	A3	20040930		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,				

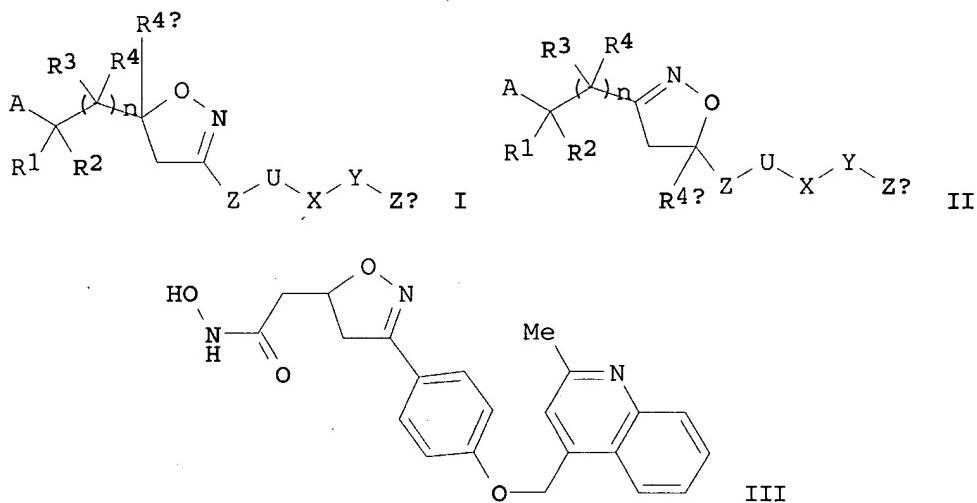
OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,  
 TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,  
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,  
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,  
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004122005 A1 20040624 US 2003-697545 20031030

PRAI US 2002-424293P P 20021106

OS MARPAT 141:7120

GI



**AB** The title isoxazoline derivs. with general formula of I and II [wherein A = (un)substituted N(OH)COH or CONHOH; U = absent, O, CO, CO<sub>2</sub>, OCO, (un)substituted NH, CH(OH), CONH, NHCO, etc.; X = absent, alkylene, alkenylene, or alkynylene; Y = absent, O, S, SO, SO<sub>2</sub>, or CO; Z = substituted carbocycle or heterocycle; Za = H, substituted carbocycle or heterocycle; R1-R4 and R4a = independently Q, alkylene-Q, alkenylene-Q, alkynylene-Q, etc.; Q = H, CHF<sub>2</sub>, CH<sub>2</sub>F, CF<sub>3</sub>, substituted carbocycle, or (hetero)cycle; n = 0 or 1] or pharmaceutically acceptable salts thereof are prepared as inhibitors of matrix metalloproteinases (MMP), TNF- $\alpha$  converting enzyme (TACE), or a combination. For example, the compound III was prepared in a multi-step synthesis. Some of compds. I have inhibitory activity with IC<sub>50</sub> of  $\leq$  0.01  $\mu$ M against metalloproteinase. I are useful for the treatment of diseases mediated by MMP and/or TACE, such as acute infection, acute phase response, age related macular degeneration, etc. (no data).

**IC** ICM A61K

**CC** 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

**ST** quinolyl isoxazoline prepn inhibitor matrix metalloproteinase TNF human

**IT** Disease, animal

(Bechet's; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

**IT** Inflammation

(Crohn's disease; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Intestine, disease  
(Crohn's; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Arthritis  
(Felty's syndrome; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Infection  
(Mycobacterial; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Arthritis  
(Reiter's syndrome; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Granulomatous disease  
(Wegener's granulomatosis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Infection  
(acute; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Inflammation  
Reproductive system, disease  
(adnexitis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Liver, disease  
(alc.; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Allergy  
(allergic asthma; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Asthma  
(allergic; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Aneurysm  
(aortic; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Disease, animal  
(arthropathy, enteropathic; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Disease, animal  
(asthenia, postradiation; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Dermatitis  
(atopic; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Hepatitis  
(autoimmune; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Fatigue, biological  
(chronic fatigue syndrome; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Eye, disease  
(cornea, ulcer; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Ulcer  
(corneal; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Joint, anatomical  
(disease, enteropathic; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Heart, disease  
(failure; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Muscle, disease

(fibromyalgia, syndrome; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Gingiva, disease

Inflammation

(gingivitis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Transplant and Transplantation

(graft-vs.-host reaction; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Injury

(hyperoxic alveolar; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Arthritis

(infectious; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Skin

(inflammatory diseases; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Rheumatoid arthritis

(juvenile; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Eye, disease

(macula, senile degeneration; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Disease, animal

(mediated by MMPs and/or TACE; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Glaucoma (disease)

(neovascular; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Lung, disease

(obstructive, chronic; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Inflammation

Periodontium, disease

(periodontitis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Bone, disease

Inflammation

(polychondritis, relapsing; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Myositis

(polymyositis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Injury

(post-ischemic reperfusion; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT AIDS (disease)

Acute-phase response

Allergy

Allergy inhibitors

Anaphylaxis

Anorexia

Anti-AIDS agents

Anti-infective agents

Anti-inflammatory agents

Antiarthritics

Antiasthmatics

Antibacterial agents

Antiglaucoma agents

Antipyretics  
Antirheumatic agents  
Antitumor agents  
Asthma  
Atherosclerosis  
Autoimmune disease  
Cachexia  
Cardiovascular agents  
Cardiovascular system, disease  
Coagulants  
Coagulation  
Dermatomyositis  
Emphysema  
Fever and Hyperthermia  
Fibrosis  
Gout  
Hemorrhage  
Human  
Immunomodulators  
Inflammation  
Lyme disease  
Meningitis  
Multiple sclerosis  
Myasthenia gravis  
Osteoarthritis  
Psoriasis  
Rheumatic fever  
Rheumatoid arthritis  
Sarcoidosis  
Shock (circulatory collapse)  
Sjogren's syndrome  
(preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)  
IT Arthritis  
(psoriatic arthritis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)  
IT Connective tissue, disease  
(scleroderma; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)  
IT Sepsis  
(sepsis syndrome; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)  
IT Neoplasm  
(solid; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)  
IT Inflammation  
Spinal column, disease  
(spondylitis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)  
IT Brain, disease  
(stroke; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)  
IT Lupus erythematosus  
(systemic; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)  
IT Inflammation  
Intestine, disease  
(ulcerative colitis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)  
IT Eye, disease  
Inflammation  
(uveitis; preparation of isoxazoline derivs. as inhibitors of MMP and/or

TACE)

IT Blood vessel, disease  
Inflammation  
(vasculitis; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT Glucocorticoids  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(withdrawal syndrome; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT 17031-92-4, Calcium pyrophosphate dihydrate  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(deposition disease; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT **694449-74-6P**  
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(drug candidate; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT **694449-26-8P 694449-28-0P 694449-30-4P**  
**694449-32-6P 694449-34-8P 694449-36-0P**  
**694449-38-2P 694449-40-6P 694449-42-8P**  
**694449-44-0P 694449-46-2P 694449-48-4P**  
**694449-50-8P 694449-52-0P 694449-54-2P**  
**694449-56-4P 694449-58-6P 694449-60-0P**  
**694449-62-2P 694449-64-4P 694449-66-6P**  
**694449-68-8P 694449-70-2P 694449-72-4P**  
**694449-76-8P 694449-78-0P 694449-80-4P**  
**694449-82-6P 694449-84-8P 694449-87-1P**  
**694449-89-3P 694449-91-7P 694449-93-9P**  
**694449-95-1P 694449-97-3P 694449-99-5P**  
**694450-01-6P 694450-03-8P 694450-05-0P**  
**694450-07-2P 694450-09-4P 694450-11-8P**  
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(drug candidate; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT 141907-41-7, Matrix metalloproteinase converting enzyme 151769-16-3, TNF- $\alpha$   
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(inhibitors; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT 53544-45-9P 65832-21-5P 66505-81-5P, 2-(Tetrahydropyran-4-ylidene)ethanol 106928-50-1P 115289-55-9P 116700-73-3P  
132079-98-2P 252722-04-6P 441774-63-6P 656803-41-7P 694450-14-1P  
694450-16-3P 694450-18-5P 694450-21-0P 694450-23-2P  
**694450-25-4P 694450-27-6P 694450-31-2P 694450-34-5P**  
694450-36-7P 694450-38-9P 694450-40-3P 694450-42-5P 694450-44-7P  
694450-46-9P 694450-48-1P 694450-50-5P 694450-52-7P 694450-54-9P  
694450-56-1P 694450-58-3P 694450-61-8P 694450-63-0P 694450-65-2P  
694450-67-4P 694450-71-0P 694450-73-2P 694450-76-5P 694450-79-8P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(intermediate; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT 78-39-7, Triethyl orthoacetate 98-01-1, Furan-2-carboxaldehyde, reactions 100-52-7, Benzaldehyde, reactions 109-90-0, Ethyl isocyanate 110-91-8, Morpholine, reactions 123-08-0, p-Hydroxybenzaldehyde 123-75-1, Pyrrolidine, reactions 527-69-5, Furan-2-carbonyl chloride

543-27-1, Isobutyl chloroformate 591-80-0, Pent-4-enoic acid 625-38-7,  
 Vinylacetic acid 1515-75-9, Penta-2,4-dienoic acid methyl ester  
 3513-81-3, 2-Methylenepropane-1,3-diol 4911-54-0, 4-Methylpent-4-enoic  
 acid ethyl ester 5621-44-3, 2-Methylenepentanedioic acid dimethyl ester  
 5927-18-4, Trimethyl phosphonoacetate 6044-68-4, 3,3-Dimethoxypropene  
 6439-57-2 7685-44-1, DL-Allylglycine 10472-24-9, Methyl  
 2-oxocyclopentanecarboxylate 18162-48-6, tert-Butyldimethylsilyl  
 chloride 24424-99-5, Di-tert-butyl dicarbonate 24731-17-7 36966-11-7  
 51747-33-2, 2-Methylbut-3-enoic acid methyl ester 57260-71-6  
 57595-23-0 62327-21-3, tert-Butyl dimethylphosphonoacetate 63721-05-1,  
 3,3-Dimethylpent-4-enoic acid methyl ester 116616-21-8 138302-49-5  
 194924-95-3 288399-19-9, 4-Chloromethyl-2-methylquinoline 441773-67-7  
 694450-87-8 694450-89-0 694450-92-5 694450-95-8

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

IT

**694449-74-6P**

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic  
 preparation); THU (Therapeutic use); BIOL (Biological study); PREP  
 (Preparation); RACT (Reactant or reagent); USES (Uses)

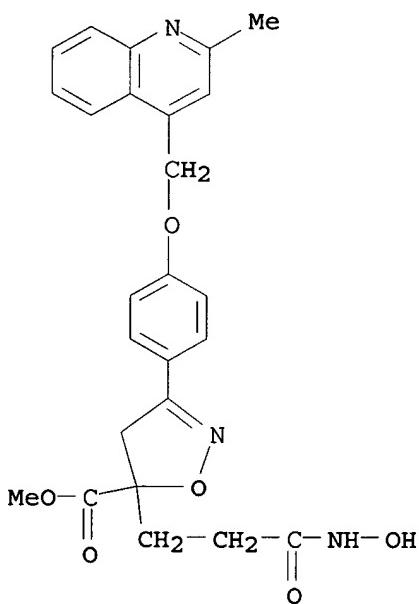
(drug candidate; preparation of isoxazoline derivs. as inhibitors of MMP  
 and/or TACE)

RN

694449-74-6 HCPLUS

CN

5-Isoxazolecarboxylic acid, 4,5-dihydro-5-[3-(hydroxyamino)-3-oxopropyl]-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-, methyl ester (9CI) (CA INDEX  
 NAME)



IT

**694449-26-8P 694449-28-0P 694449-30-4P**

**694449-32-6P 694449-34-8P 694449-36-0P**

**694449-38-2P 694449-40-6P 694449-42-8P**

**694449-44-0P 694449-46-2P 694449-48-4P**

**694449-50-8P 694449-52-0P 694449-54-2P**

**694449-56-4P 694449-58-6P 694449-60-0P**

**694449-62-2P 694449-64-4P 694449-66-6P**

**694449-68-8P 694449-70-2P 694449-72-4P**

**694449-76-8P 694449-78-0P 694449-80-4P**

**694449-82-6P 694449-84-8P 694449-87-1P**

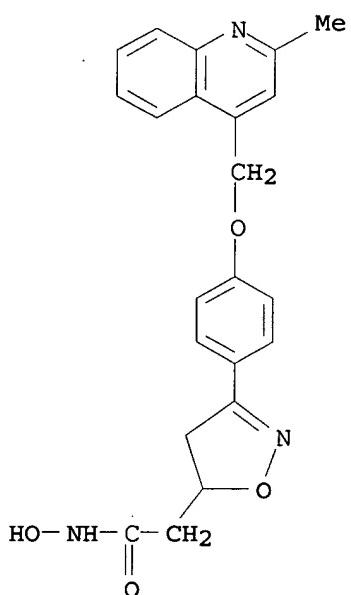
694449-89-3P 694449-91-7P 694449-93-9P  
 694449-95-1P 694449-97-3P 694449-99-5P  
 694450-01-6P 694450-03-8P 694450-05-0P  
 694450-07-2P 694450-09-4P 694450-11-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

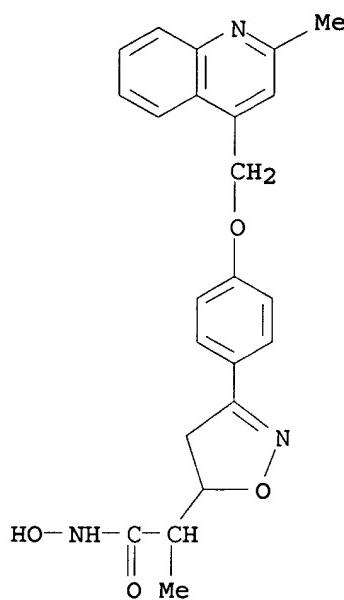
RN 694449-26-8 HCPLUS

CN 5-Isoxazoleacetamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 694449-28-0 HCPLUS

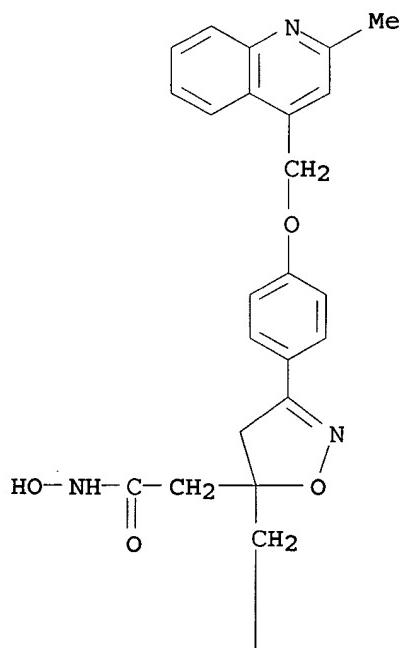
CN 5-Isoxazoleacetamide, 4,5-dihydro-N-hydroxy- $\alpha$ -methyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



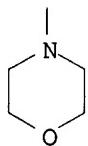
RN 694449-30-4 HCPLUS

CN 5-Isoxazoleacetamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-(4-morpholinylmethyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



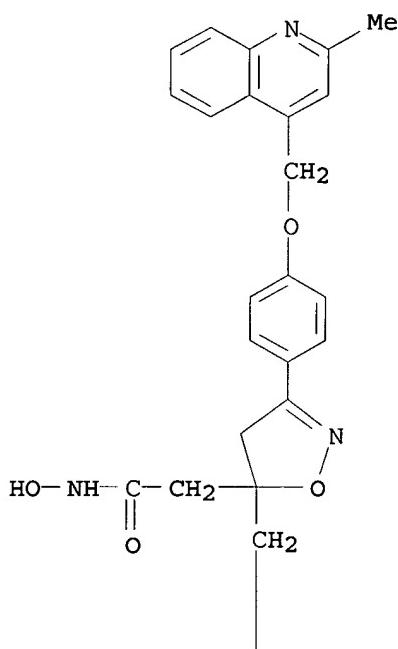
PAGE 2-A



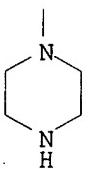
RN 694449-32-6 HCAPLUS

CN 5-Isoxazoleacetamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-(1-piperazinylmethyl)- (9CI) (CA INDEX NAME)

PAGE 1-A

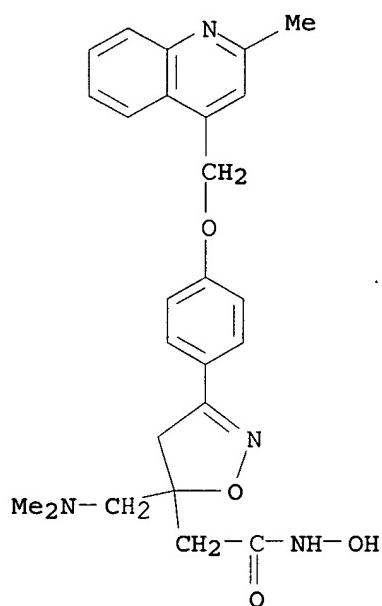


PAGE 2-A



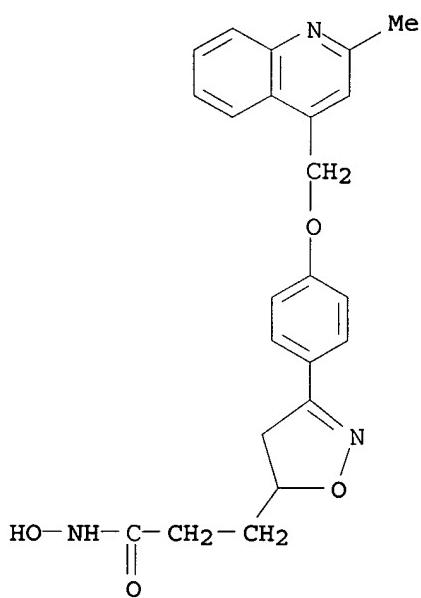
RN 694449-34-8 HCAPLUS

CN 5-Isoxazoleacetamide, 5-[(dimethylamino)methyl]-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



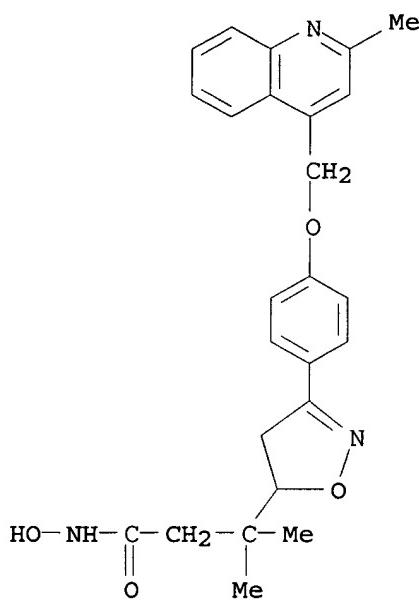
RN 694449-36-0 HCAPLUS

CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 694449-38-2 HCAPLUS

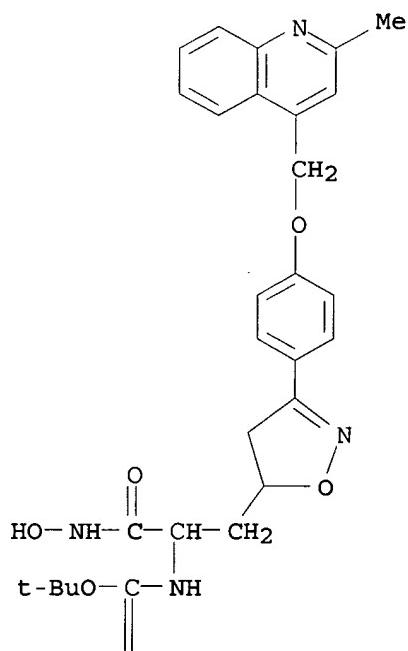
CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-β,β-dimethyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



RN 694449-40-6 HCPLUS

CN Carbamic acid, [1-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]methyl]-2-(hydroxyamino)-2-oxoethyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

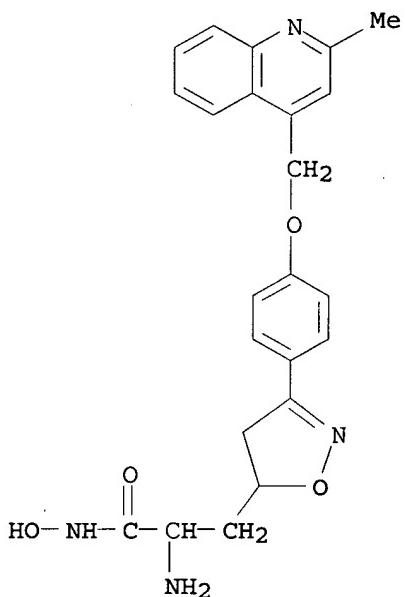
PAGE 1-A



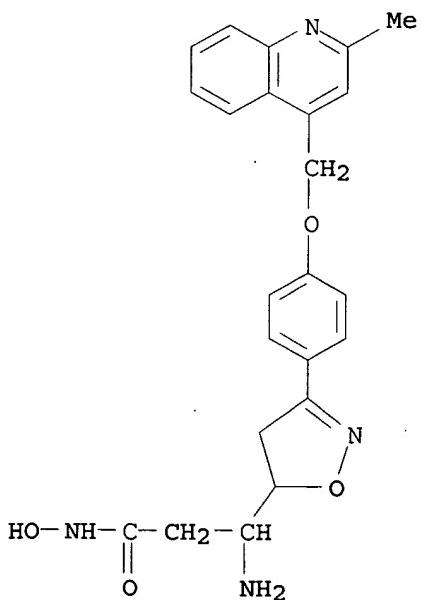
PAGE 2-A



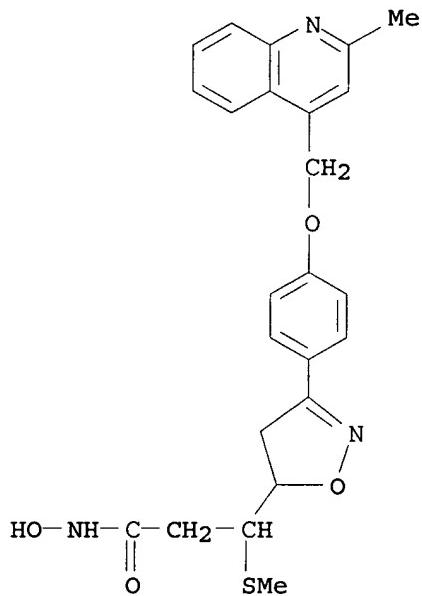
RN 694449-42-8 HCAPLUS

CN 5-Isoxazolepropanamide,  $\alpha$ -amino-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)

RN 694449-44-0 HCAPLUS

CN 5-Isoxazolepropanamide,  $\beta$ -amino-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)

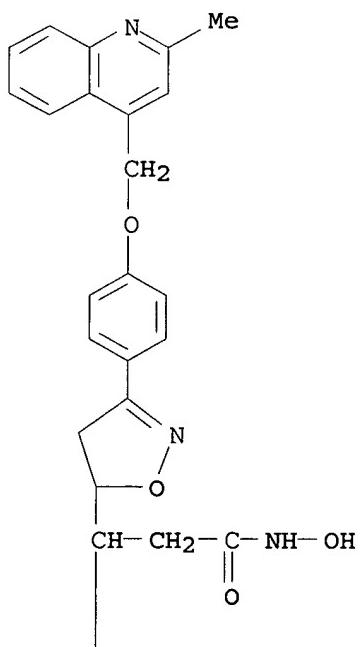
RN 694449-46-2 HCAPLUS

CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- $\beta$ -(methylthio)- (9CI) (CA INDEX NAME)

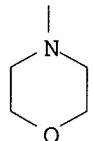
RN 694449-48-4 HCAPLUS

CN 4-Morpholinepropanamide,  $\beta$ -[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-N-hydroxy- (9CI) (CA INDEX NAME)

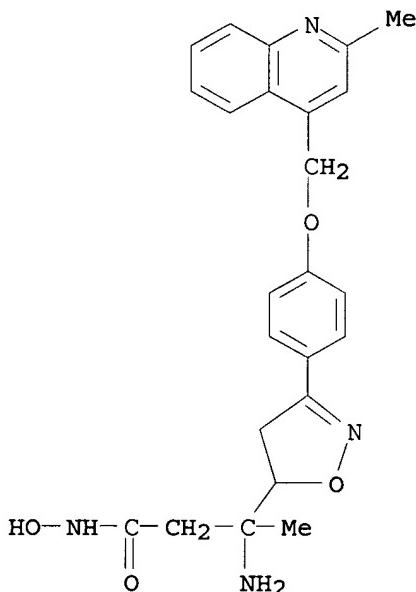
PAGE 1-A



PAGE 2-A

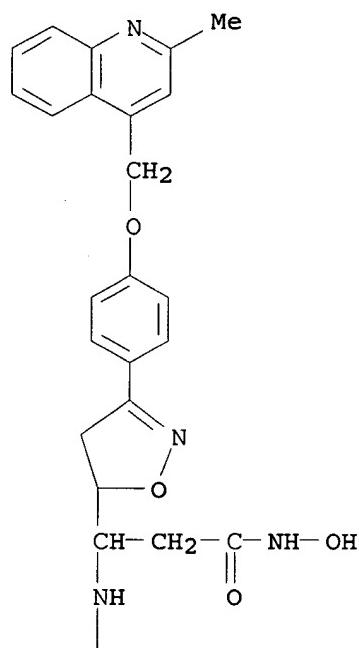


RN 694449-50-8 HCAPLUS  
 CN 5-Isoxazolepropanamide,  $\beta$ -amino-4,5-dihydro-N-hydroxy- $\beta$ -methyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)

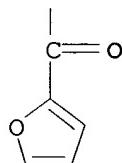


RN 694449-52-0 HCAPLUS  
 CN 5-Isoxazolepropanamide,  $\beta$ -[(2-furanylcarbonyl)amino]-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



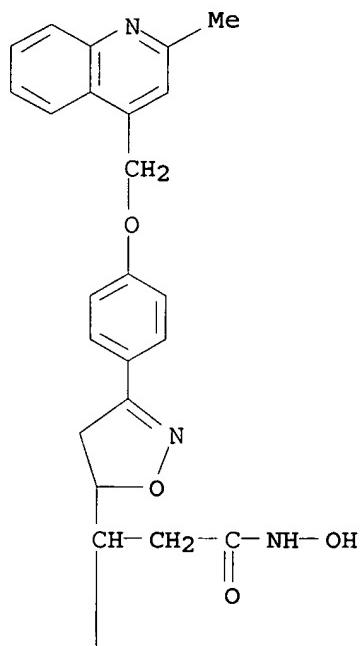
PAGE 2-A



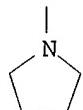
RN 694449-54-2 HCPLUS

CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-beta-1-pyrrolidinyl- (9CI) (CA INDEX NAME)

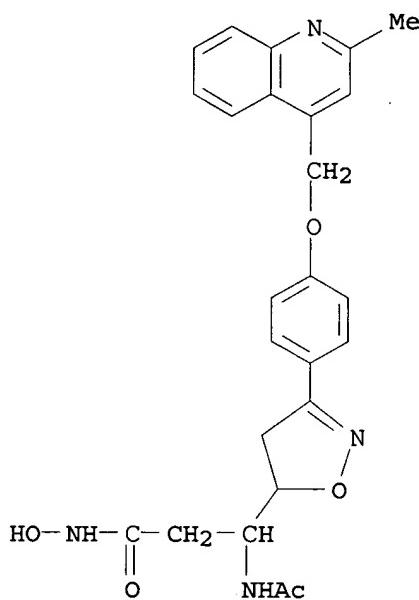
PAGE 1-A



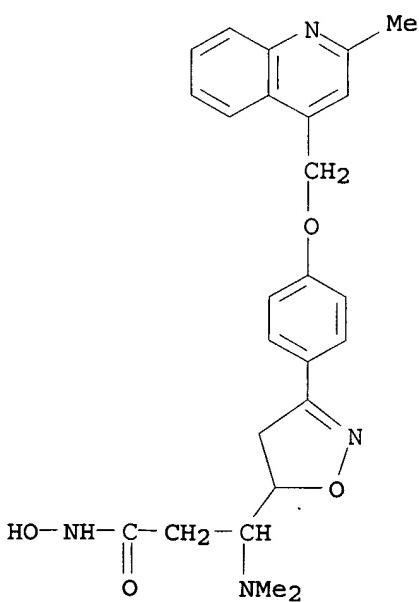
PAGE 2-A



RN 694449-56-4 HCAPLUS  
CN 5-Isoxazolepropanamide, β-(acetylamino)-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



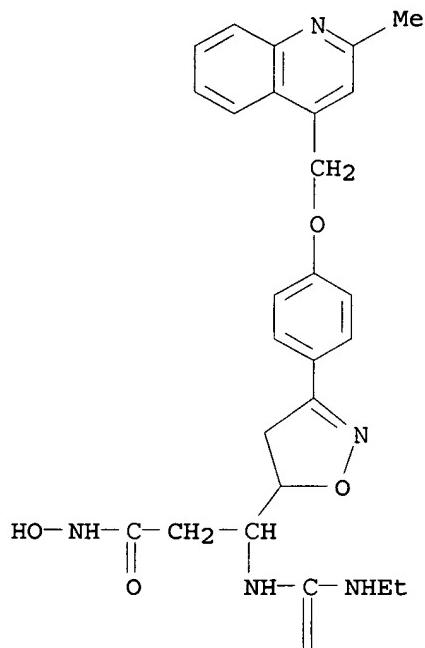
RN 694449-58-6 HCPLUS

CN 5-Isoxazolepropanamide,  $\beta$ -(dimethylamino)-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)

RN 694449-60-0 HCPLUS

CN 5-Isoxazolepropanamide,  $\beta$ -[(ethylamino)carbonyl]amino)-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

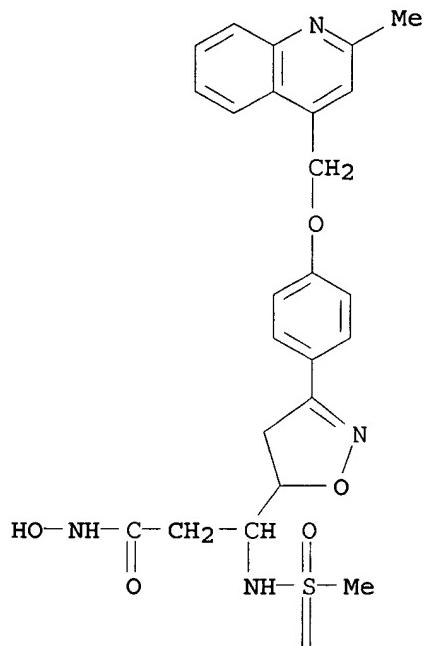


PAGE 2-A



RN 694449-62-2 HCPLUS  
CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-β-[(methylsulfonyl)amino]- (9CI) (CA INDEX NAME)

PAGE 1-A

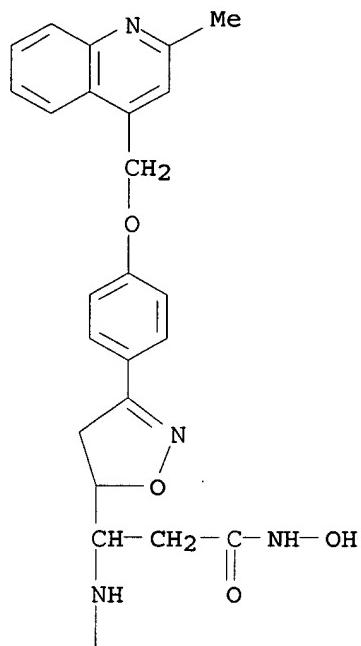


PAGE 2-A

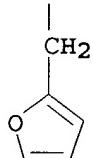


RN 694449-64-4 HCAPLUS  
CN 5-Isoxazolepropanamide,  $\beta$ -[(2-furanyl methyl) amino]-4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

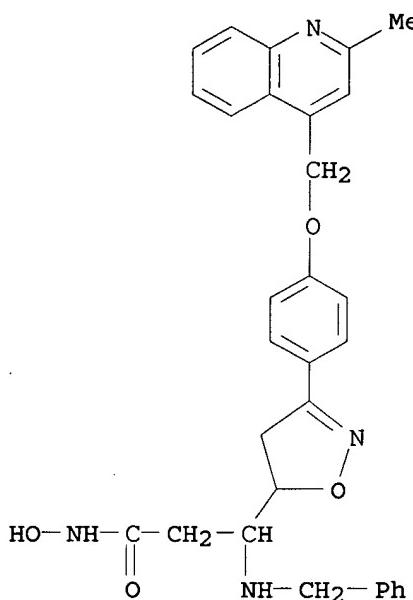


PAGE 2-A



RN 694449-66-6 HCPLUS

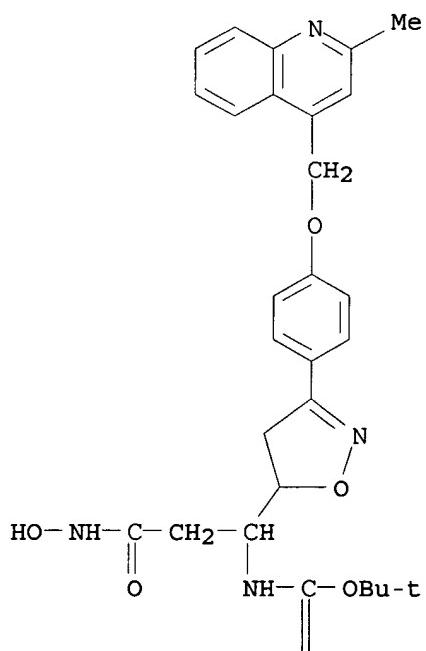
CN 5-Isoazolepropanamide, 4,5-dihydro-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-β-[(phenylmethyl)amino]- (9CI) (CA INDEX NAME)



RN 694449-68-8 HCAPLUS

CN Carbamic acid, [1-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-3-(hydroxyamino)-3-oxopropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

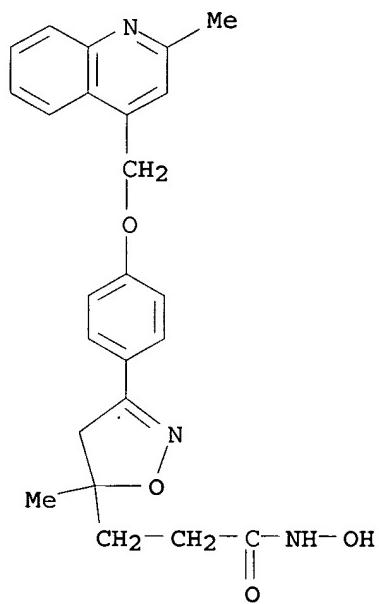
PAGE 1-A



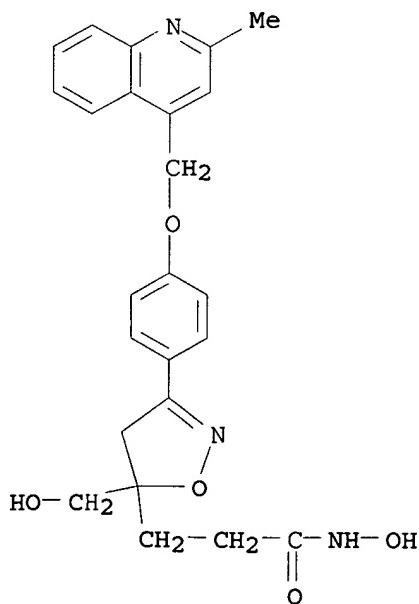
PAGE 2-A



RN 694449-70-2 HCPLUS  
 CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-5-methyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)

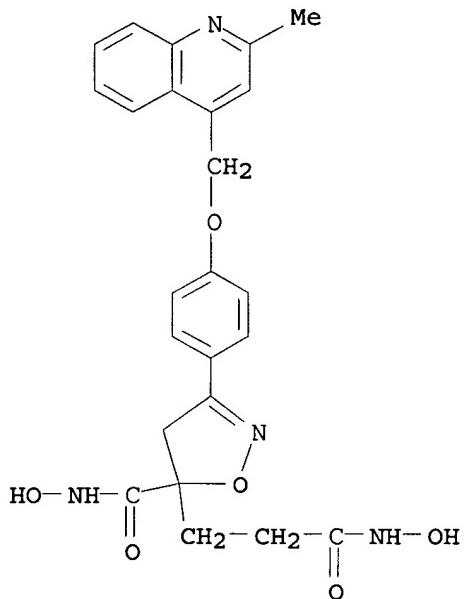


RN 694449-72-4 HCPLUS  
 CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-5-(hydroxymethyl)-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



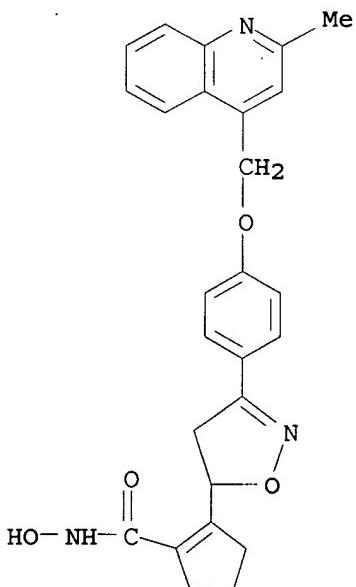
RN 694449-76-8 HCAPLUS

CN 5-Isoxazolepropanamide, 4,5-dihydro-N-hydroxy-5-[(hydroxyamino)carbonyl]-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



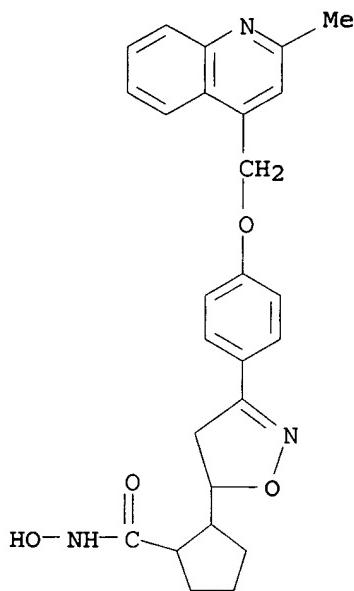
RN 694449-78-0 HCAPLUS

CN 1-Cyclopentene-1-carboxamide, 2-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-N-hydroxy- (9CI) (CA INDEX NAME)



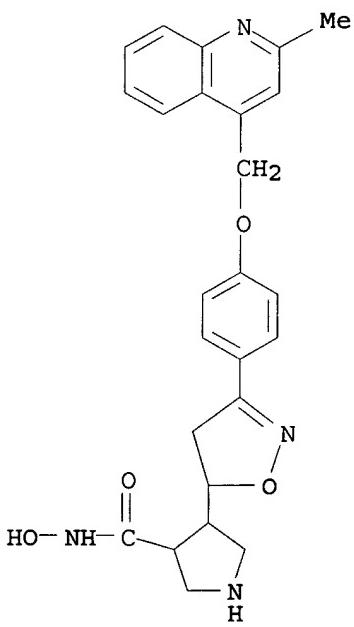
RN 694449-80-4 HCAPLUS

CN Cyclopentanecarboxamide, 2-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-N-hydroxy- (9CI) (CA INDEX NAME)



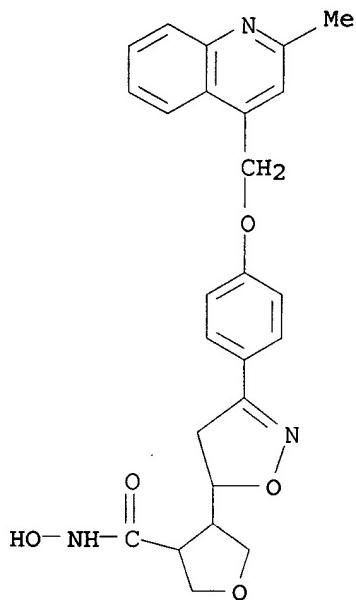
RN 694449-82-6 HCPLUS

CN 3-Pyrrolidinecarboxamide, 4-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-N-hydroxy- (9CI) (CA INDEX NAME)



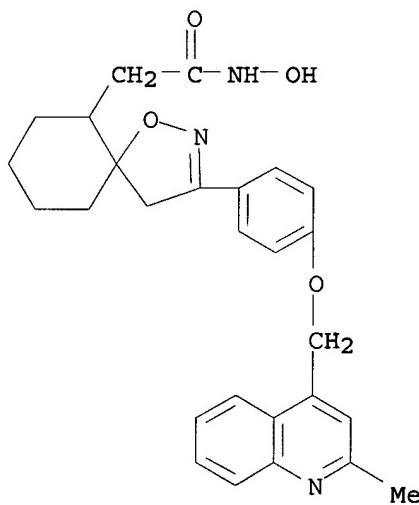
RN 694449-84-8 HCPLUS

CN 3-Furancarboxamide, 4-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]tetrahydro-N-hydroxy- (9CI) (CA INDEX NAME)



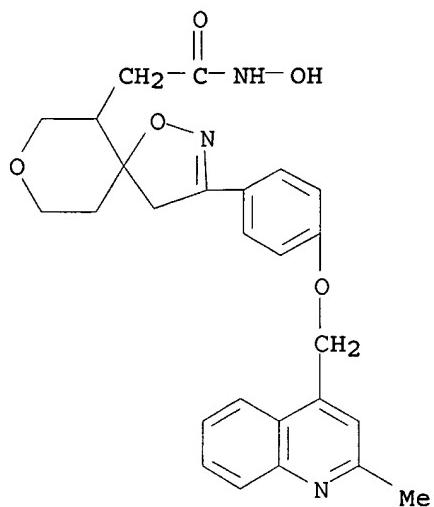
RN 694449-87-1 HCPLUS

CN 1-Oxa-2-azaspiro[4.5]dec-2-ene-6-acetamide, N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



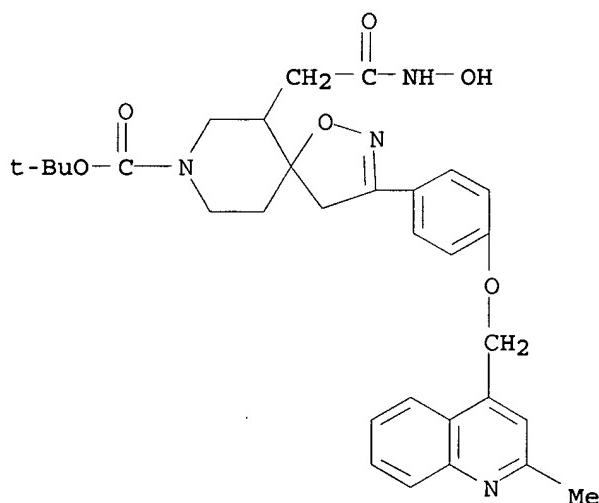
RN 694449-89-3 HCPLUS

CN 1,8-Dioxa-2-azaspiro[4.5]dec-2-ene-6-acetamide, N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



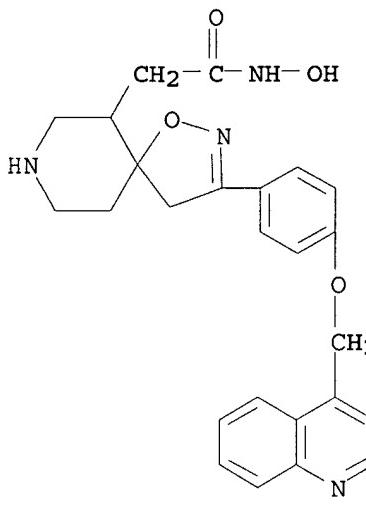
RN 694449-91-7 HCAPLUS

CN 1-Oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylic acid, 6-[2-(hydroxyamino)-2-oxoethyl]-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



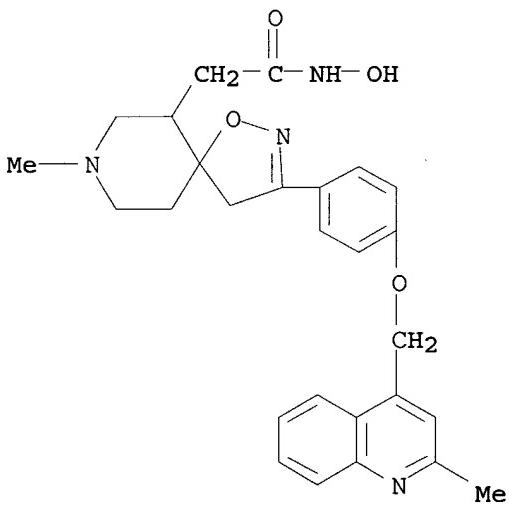
RN 694449-93-9 HCAPLUS

CN 1-Oxa-2,8-diazaspiro[4.5]dec-2-ene-6-acetamide, N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



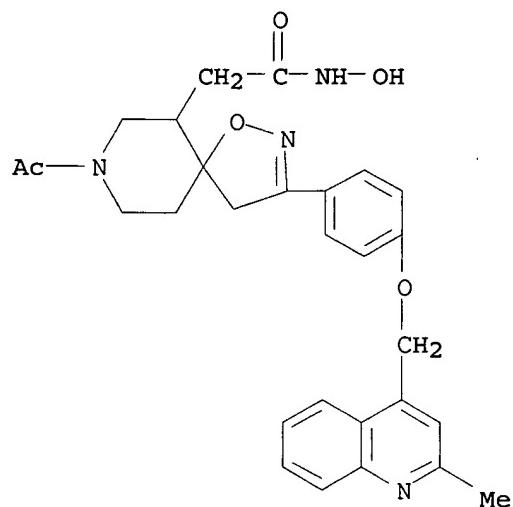
RN 694449-95-1 HCPLUS

CN 1-Oxa-2,8-diazaspiro[4.5]dec-2-ene-6-acetamide, N-hydroxy-8-methyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



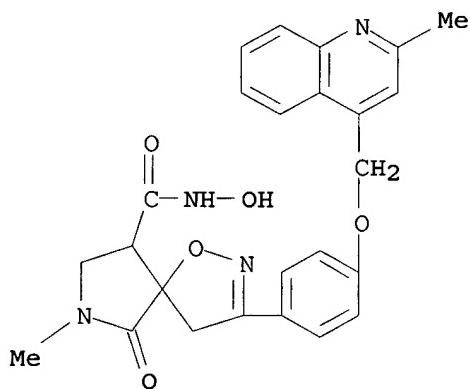
RN 694449-97-3 HCPLUS

CN 1-Oxa-2,8-diazaspiro[4.5]dec-2-ene-6-acetamide, 8-acetyl-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]- (9CI) (CA INDEX NAME)



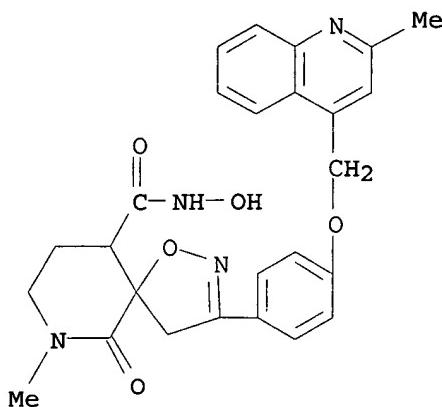
RN 694449-99-5 HCAPLUS

CN 1-Oxa-2,7-diazaspiro[4.4]non-2-ene-9-carboxamide, N-hydroxy-7-methyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-6-oxo- (9CI) (CA INDEX NAME)



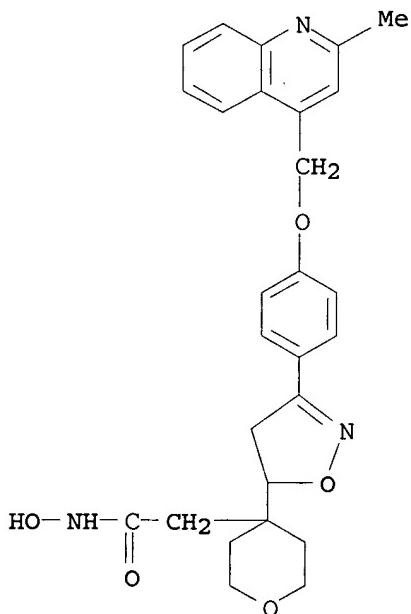
RN 694450-01-6 HCAPLUS

CN 1-Oxa-2,7-diazaspiro[4.5]dec-2-ene-10-carboxamide, N-hydroxy-7-methyl-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-6-oxo- (9CI) (CA INDEX NAME)



RN 694450-03-8 HCPLUS

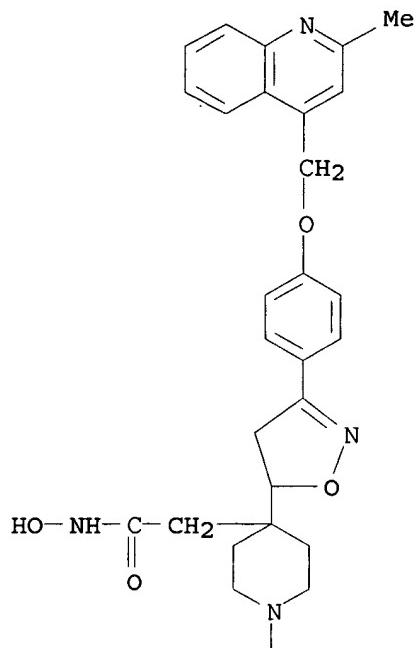
CN 2H-Pyran-4-acetamide, 4-[4,5-dihydro-3-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyltetrahydro-N-hydroxy- (9CI) (CA INDEX NAME)



RN 694450-05-0 HCPLUS

CN 4-Piperidineacetamide, 1-acetyl-4-[4,5-dihydro-3-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl-N-hydroxy- (9CI) (CA INDEX NAME)

PAGE 1-A



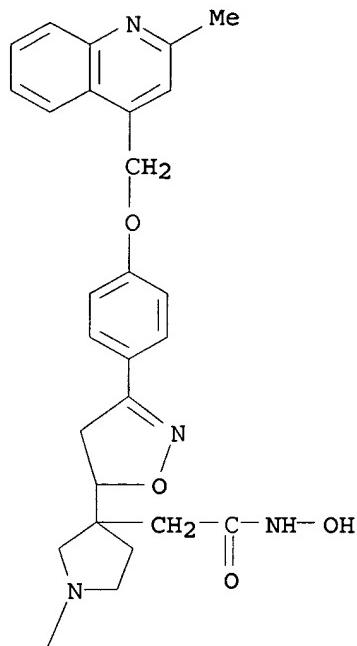
PAGE 2-A



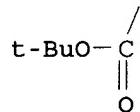
RN 694450-07-2 HCPLUS

CN 1-Pyrrolidinecarboxylic acid, 3-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-3-[2-(hydroxyamino)-2-oxoethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

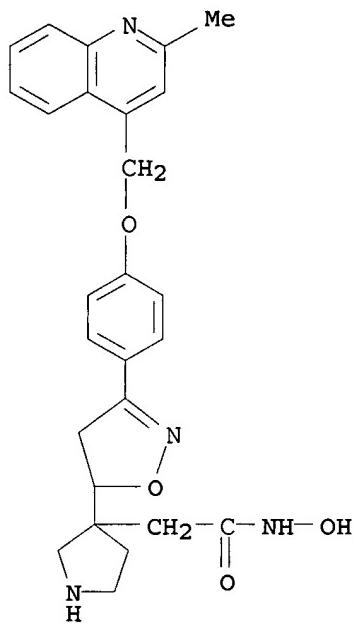
PAGE 1-A



PAGE 2-A

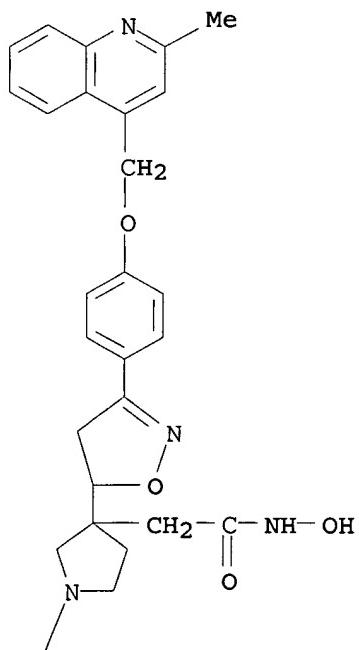


RN 694450-09-4 HCPLUS  
CN 3-Pyrrolidineacetamide, 3-[4,5-dihydro-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]-N-hydroxy- (9CI) (CA INDEX NAME)



RN 694450-11-8 HCPLUS  
CN 3-Pyrrolidineacetamide, 3-[4,5-dihydro-3-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl-N-hydroxy-1-methyl- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



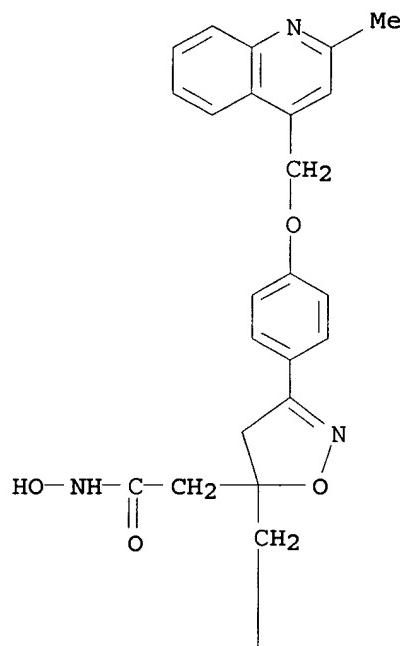
IT 694450-25-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (intermediate; preparation of isoxazoline derivs. as inhibitors of MMP and/or TACE)

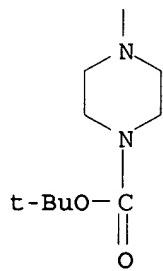
RN 694450-25-4 HCPLUS

CN 1-Piperazinecarboxylic acid, 4-[[4,5-dihydro-5-[2-(hydroxyamino)-2-oxoethyl]-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-5-isoxazolyl]methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



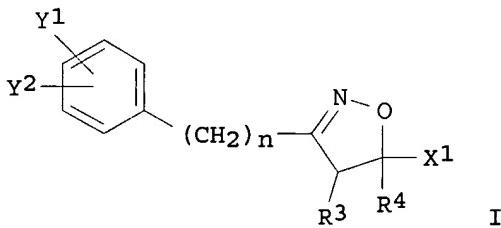
PAGE 2-A



L7 ANSWER 2 OF 6 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 2000:623742 HCPLUS  
 DN 133:222722  
 TI Preparation of isoxazoline compounds as inhibitors of TNF release  
 IN Cohan, Victoria Lee; Kleinman, Edward Fox  
 PA Pfizer Inc., USA  
 SO U.S., 19 pp.  
 CODEN: USXXAM  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6114367	A	20000905	US 1998-187833	19981106
PRAI	US 1998-187833				
OS	MARPAT 133:222722		19981106		

GI



AB Isoxazolines I [X1 = (CH<sub>2</sub>)<sub>q</sub>OH, CH<sub>2</sub>R<sub>5</sub>OH, (CH<sub>2</sub>)<sub>m</sub>CONR<sub>6</sub>OH; n 0-3; Y<sub>1</sub>, Y<sub>2</sub> = H, alkyl, phenylalkyl, CHF<sub>2</sub>, etc.; R<sub>3</sub> = alkyl, phenylalkyl, CF<sub>3</sub>, etc.; R<sub>4</sub> = H, alkyl, Ph, etc.], inhibitors of tumor necrosis factor (no data), were prepared E.g., 3-(3-cyclopentyloxy-4-methoxy)phenyl-2-isoxazoline-5-hydroxamic acid was prepared

IC ICM A61K031-42  
 ICS A61K031-47

INCL 514378000

CC 28-6 (Heterocyclic Compounds (More Than One Hetero Atom))  
 Section cross-reference(s): 1

ST isoxazoline prepn TNF release inhibitor

IT Tumor necrosis factors  
 RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)  
 (preparation of isoxazolines as inhibitors of TNF release)

IT 167098-70-6P 167098-73-9P 167098-74-0P 167098-75-1P  
 167098-76-2P 167098-77-3P 167098-78-4P 167098-79-5P  
 167098-80-8P 167098-81-9P 167098-82-0P 167098-83-1P 167098-84-2P  
 167098-85-3P 167098-86-4P 167098-87-5P  
 167098-88-6P 167098-89-7P 167098-92-2P 167098-93-3P  
 167099-58-3P 167099-60-7P 172678-99-8P 290370-53-5P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of isoxazolines as inhibitors of TNF release)

IT 96-33-3, Methyl acrylate 96-41-3, Cyclopentanol 97-63-2, Ethyl methacrylate 100-39-0, Benzyl bromide 100-83-4, 3-Hydroxybenzaldehyde 121-33-5, Vanillin 123-08-0, 4-Hydroxybenzaldehyde 140-88-5, Ethyl acrylate 621-59-0, Isovanillin 623-70-1, Ethyl trans-crotonate

627-27-0, 3-Buten-1-ol 814-68-6, Acryloyl chloride 2323-74-2  
 2327-69-7 2627-86-3, (S)- $\alpha$ -Methylbenzylamine 4377-41-7,  
 2-Chloromethylquinoline 10521-91-2, 5-Phenyl-1-pentanol 17145-91-4,  
 Triethyl 2-phosphonobutyrate 25662-28-6 31641-78-8 94594-90-8  
 108448-77-7 290370-54-6 290370-55-7

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of isoxazolines as inhibitors of TNF release)

IT 699-06-9P 3070-65-3P 3550-06-9P 3618-37-9P 22286-82-4P  
 50899-14-4P 51673-94-0P 94594-91-9P 119944-89-7P 158429-65-3P  
 162279-48-3P 167098-71-7P 167098-94-4P 167098-95-5P 167098-96-6P  
 167098-97-7P 167098-98-8P 167098-99-9P 167099-00-5P 167099-01-6P  
 167099-02-7P 167099-03-8P 167099-04-9P 167099-05-0P 167099-06-1P  
 167099-07-2P 167099-08-3P 167099-09-4P 167099-10-7P 167099-11-8P  
 167099-12-9P 167099-13-0P 167099-15-2P 167099-16-3P 167099-17-4P  
 167099-18-5P 167099-20-9P 167099-21-0P 172679-04-8P 172679-07-1P  
 203062-84-4P 203062-86-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of isoxazolines as inhibitors of TNF release)

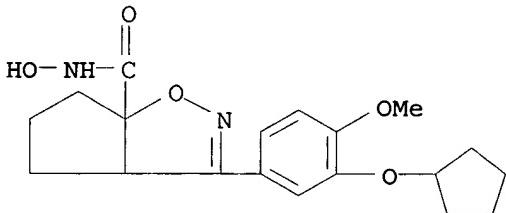
IT 167098-70-6P 167098-75-1P 167098-76-2P  
 167098-85-3P 167098-86-4P 167098-87-5P  
 167098-92-2P 167098-93-3P 172678-99-8P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of isoxazolines as inhibitors of TNF release)

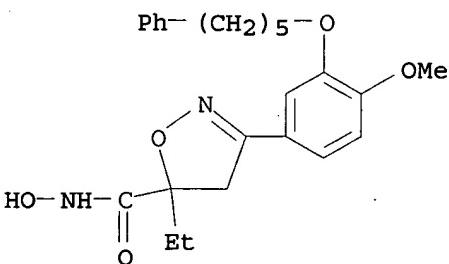
RN 167098-70-6 HCPLUS

CN 6aH-Cyclopent[d]isoxazole-6a-carboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-3a,4,5,6-tetrahydro-N-hydroxy- (9CI) (CA INDEX NAME)



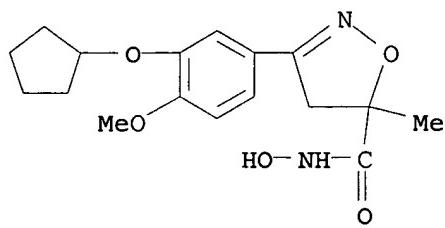
RN 167098-75-1 HCPLUS

CN 5-Isoxazolecarboxamide, 5-ethyl-4,5-dihydro-N-hydroxy-3-[4-methoxy-3-[(5-phenylpentyl)oxy]phenyl]- (9CI) (CA INDEX NAME)



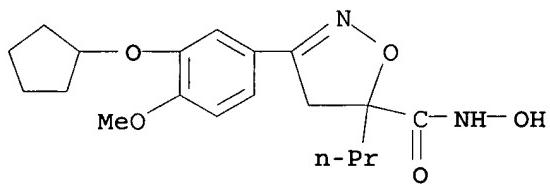
RN 167098-76-2 HCPLUS

CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl- (9CI) (CA INDEX NAME)



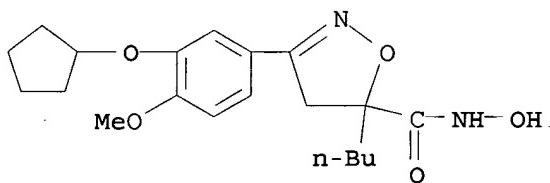
RN 167098-85-3 HCPLUS

CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-propyl- (9CI) (CA INDEX NAME)



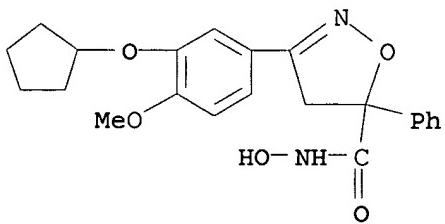
RN 167098-86-4 HCPLUS

CN 5-Isoxazolecarboxamide, 5-butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)



RN 167098-87-5 HCPLUS

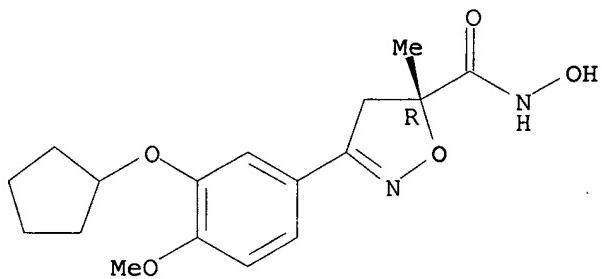
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-phenyl- (9CI) (CA INDEX NAME)



RN 167098-92-2 HCPLUS

CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5R)- (9CI) (CA INDEX NAME)

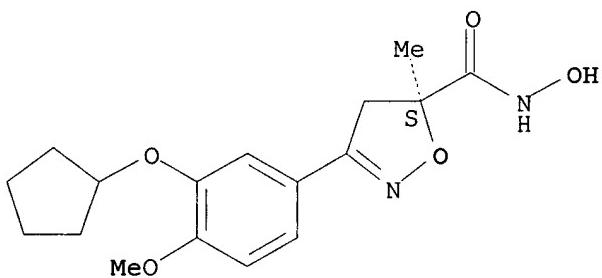
Absolute stereochemistry.



RN 167098-93-3 HCAPLUS

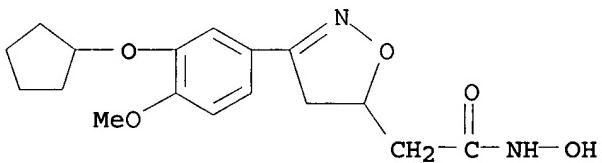
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 172678-99-8 HCAPLUS

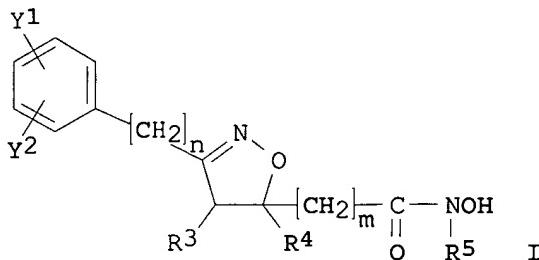
CN 5-Isoxazoleacetamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 1998:118606 HCAPLUS  
 DN 128:180405  
 TI Preparation of isoxazolines as antiinflammatory agents  
 IN Kleinman, Edward Fox  
 PA Pfizer Inc., USA  
 SO U.S., 15 pp., Cont.-in-part of U.S. Ser. No. 262,086, abandoned.  
 CODEN: USXXAM  
 DT Patent  
 LA English  
 FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	-----	-----	-----	-----

PI	US 5716967	A	19980210	US 1996-640944	19960515
	WO 9514681	A1	19950601	WO 1994-IB333	19941026
	W: AU, BR, CA, CN, CZ, HU, JP, KR, NO, NZ, PL, RU, US, US RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	ZA 9409379	A	19960527	ZA 1994-9379	19941125
PRAI	US 1993-157248	B2	19931126		
	US 1994-262086	B2	19940617		
	WO 1994-IB333	W	19941026		
OS	MARPAT 128:180405				
GI					



**AB** The title compds. [I; m, n = 0-3; Y1, Y2 = H, C1-6 alkyl, (un)substituted phenylalkyl, etc.; R3 = H, C1-3 alkyl, fluoro(C1-3)alkyl, etc.; R4 = H, C1-5 alkyl, fluoro(C1-5)alkyl, etc.; R3R4 together with the carbon atoms to which they are attached = carbocyclic ring having 4-7 carbon atoms; R5 = H, C1-3 alkyl], which are selective inhibitors of phosphodiesterase type IV (PDE IV) and therefore useful in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, dermatitis, shock, atopic dermatitis, rheumatoid arthritis and osteoarthritis, were prepared. Thus, treatment of Et 3-(4-methoxy-3-cyclopentyloxy)-2-isoxazoline-5-carboxylate with H<sub>2</sub>NOH.HCl in the presence of NaOMe in MeOH afforded I [Y1 = 4-MeO; Y2 = 3-cyclopentyloxy; R3-R5 = H; n = m = 0]. Compds. I are effective in treatment of inflammatory conditions at 0.1-500 mg/day for an average adult patient (70 kg).

**IC** ICM C07D261-04  
ICS A61K031-42

**INCL** 514313000

**CC** 28-6 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1

**ST** isoxazoline prepn antiinflammatory phosphodiesterase selective inhibitor

**IT** Anti-inflammatory agents  
(preparation of isoxazolines as antiinflammatory agents)

**IT** 167098-70-6P 167098-73-9P 167098-74-0P 167098-75-1P  
167098-76-2P 167098-77-3P 167098-78-4P 167098-79-5P  
167098-80-8P 167098-81-9P 167098-82-0P 167098-83-1P 167098-84-2P  
167098-85-3P 167098-86-4P 167098-87-5P  
167098-88-6P 167098-89-7P 167098-92-2P 167098-93-3P  
172678-99-8P 172679-00-4P

**RL:** BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of isoxazolines as antiinflammatory agents)

**IT** 96-33-3, Methyl acrylate 96-41-3, Cyclopentanol 97-63-2, Ethyl methacrylate 100-39-0, Benzyl bromide 100-83-4 121-33-5, Vanillin 123-08-0, p-Hydroxybenzaldehyde 140-88-5, Ethyl acrylate 621-59-0, Isovanillin 627-27-0, But-1-en-4-ol 814-68-6, Acryloyl chloride

932-90-1, Benzaldehyde oxime 2323-74-2, Triethyl phosphonopentanoate  
 2627-86-3, (S)-(-)- $\alpha$ -Methylbenzylamine 4134-14-9 4377-41-7,  
 2-(Chloromethyl)quinoline 10521-91-2, 5-Phenyl-1-pentanol 10544-63-5,  
 Ethyl crotonate 17145-91-4, Triethyl 2-phosphonobutyrate 25662-28-6,  
 Methyl 1-cyclopentenoate 31641-78-8, Triethyl phosphonophenylacetate  
 108448-77-7

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of isoxazolines as antiinflammatory agents)

IT 699-06-9P 3070-65-3P 3550-06-9P 3618-37-9P 22286-82-4P  
 50899-14-4P 51673-94-0P 119944-89-7P 158429-65-3P 162279-48-3P  
 167098-71-7P 167098-94-4P 167098-95-5P 167098-96-6P 167098-97-7P  
 167098-98-8P 167098-99-9P 167099-00-5P 167099-01-6P 167099-02-7P  
 167099-03-8P 167099-04-9P 167099-05-0P 167099-06-1P 167099-07-2P  
 167099-08-3P 167099-09-4P 167099-10-7P 167099-11-8P 167099-12-9P  
 167099-13-0P 167099-15-2P 167099-16-3P 167099-17-4P 167099-18-5P  
 167099-19-6P 167099-20-9P 167099-21-0P 172679-04-8P 203062-84-4P  
 203062-86-6P 203062-88-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of isoxazolines as antiinflammatory agents)

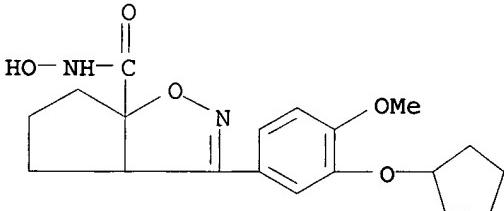
IT 9036-21-9  
 RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)  
 (selective inhibitors of PDE IV; preparation of isoxazolines as antiinflammatory agents)

IT 167098-70-6P 167098-75-1P 167098-76-2P  
 167098-85-3P 167098-86-4P 167098-87-5P  
 167098-92-2P 167098-93-3P 172678-99-8P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of isoxazolines as antiinflammatory agents)

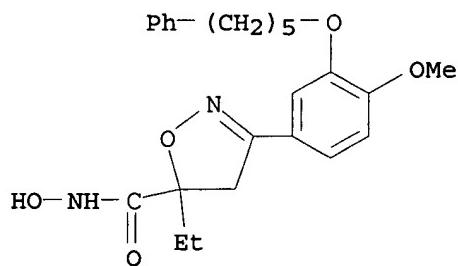
RN 167098-70-6 HCPLUS

CN 6aH-Cyclopent[d]isoxazole-6a-carboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-3a,4,5,6-tetrahydro-N-hydroxy- (9CI) (CA INDEX NAME)

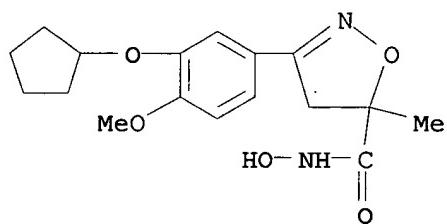


RN 167098-75-1 HCPLUS

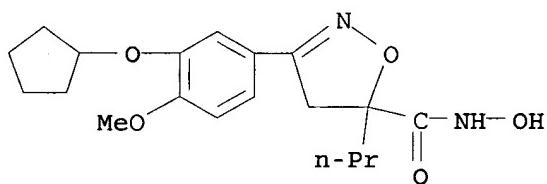
CN 5-Isoxazolecarboxamide, 5-ethyl-4,5-dihydro-N-hydroxy-3-[4-methoxy-3-[(5-phenylpentyl)oxy]phenyl]- (9CI) (CA INDEX NAME)



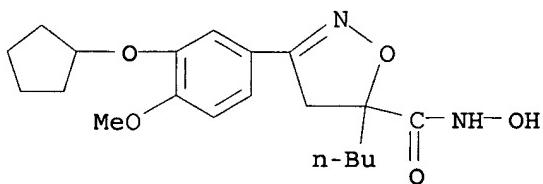
RN 167098-76-2 HCAPLUS  
 CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-  
 N-hydroxy-5-methyl- (9CI) (CA INDEX NAME)



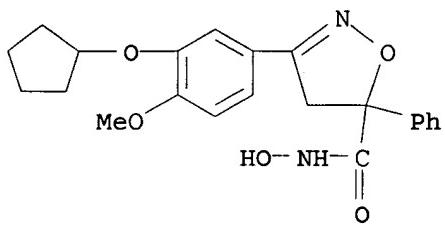
RN 167098-85-3 HCAPLUS  
 CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-  
 N-hydroxy-5-propyl- (9CI) (CA INDEX NAME)



RN 167098-86-4 HCAPLUS  
 CN 5-Isoxazolecarboxamide, 5-butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)



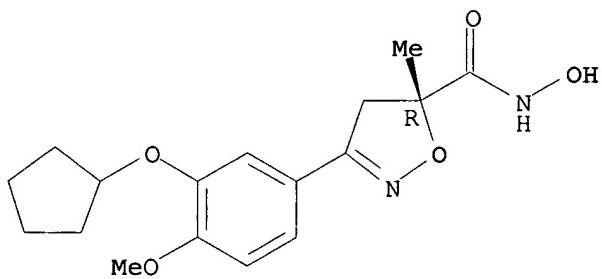
RN 167098-87-5 HCAPLUS  
 CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-  
 N-hydroxy-5-phenyl- (9CI) (CA INDEX NAME)



RN 167098-92-2 HCAPLUS

CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5R)- (9CI) (CA INDEX NAME)

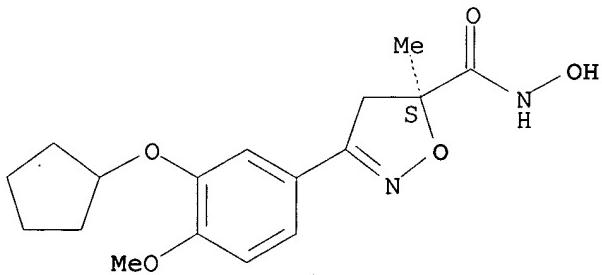
Absolute stereochemistry.



RN 167098-93-3 HCAPLUS

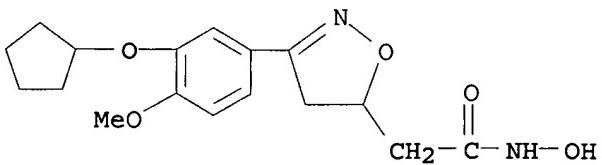
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 172678-99-8 HCAPLUS

CN 5-Isoxazoleacetamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)



RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD

## ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 6 HCPLUS COPYRIGHT 2006 ACS on STN  
AN 1998:43032 HCPLUS  
DN 128:188289  
TI Striking Effect of Hydroxamic Acid Substitution on the Phosphodiesterase Type 4 (PDE4) and TNF $\alpha$  Inhibitory Activity of Two Series of Rolipram Analogs: Implications for a New Active Site Model of PDE4  
AU Kleinman, Edward F.; Campbell, Erin; Giordano, Lisa A.; Cohan, Victoria L.; Jenkinson, Teresa H.; Cheng, John B.; Shirley, John T.; Pettipher, E. Roy; Salter, Eben D.; Hibbs, Tessa A.; DiCapua, Frank M.; Bordner, John  
CS Central Research Division, Pfizer Inc, Groton, CT, 06340, USA  
SO Journal of Medicinal Chemistry (1998), 41(3), 266-270  
CODEN: JMCMAR; ISSN: 0022-2623  
PB American Chemical Society  
DT Journal  
LA English  
AB 3-Aryl-2-isoxazoline-5-hydroxamic acids and their acyclic variant N-aryl amino hydroxamic acids, patterned after the archetypal phosphodiesterase type 4 (PDE4) inhibitor rolipram, are potent inhibitors of human monocyte (HM) cytosol PDE and LPS-induced release of TNF $\alpha$  in HM and human whole blood (HWB). The SARs of the two series, which run parallel, demonstrates that the hydroxamic acid makes a unique, tight, and highly stereospecific interaction with PDE4. The most potent analog, CP-293121 (I), is 100-fold more potent than rolipram in the HM-PDE4 assay. The therapeutic potential of these compds. in diseases associated with the overprodn. of TNF $\alpha$  is reflected in the IC50 of I in the HWB-TNF $\alpha$  assay, which is 30 nM and to our knowledge is the lowest of any PDE4 inhibitor known. The close structural resemblance of the noncatechol regions of these series to the ribose-3',5'-phosphate group of cAMP as is putatively bound to a divalent metal ion in the active site provides circumstantial evidence that they bind to PDE4, in part, as substrate analogs of cAMP, which has interesting implications for a new active site model of PDE4.  
CC 1-3 (Pharmacology)  
Section cross-reference(s): 7, 27  
ST hydroxamate prepn phosphodiesterase TNF alpha structure; phosphodiesterase 4 inhibitor hydroxamate structure activity; TNF alpha hydroxamate structure activity  
IT Enzyme functional sites  
(active; preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF- $\alpha$ )  
IT Cytoplasm  
(cytosol; preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF- $\alpha$ )  
IT Blood  
Monocyte  
(preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF- $\alpha$ )  
IT Tumor necrosis factors  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF- $\alpha$ )  
IT 167098-73-9P 167098-76-2P 167098-77-3P 167098-85-3P  
167098-88-6P 167098-89-7P 167098-92-2P 167098-93-3P  
172678-99-8P 188030-12-8P 188030-18-4P 188030-20-8P  
188030-31-1P 188030-32-2P 188030-41-3P 203643-42-9P  
203643-46-3P 203643-48-5P  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF- $\alpha$ )

IT 9036-21-9, CAMP phosphodiesterase  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF- $\alpha$ )

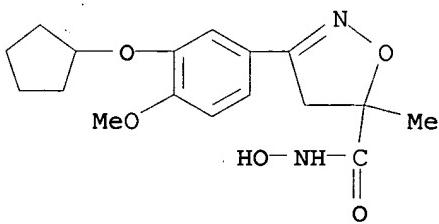
IT 4519-46-4, Methyl  $\alpha$ -bromoacrylate 63648-89-5 79722-09-1  
 79722-10-4 144036-17-9 162279-48-3 167099-77-6 188029-65-4  
 203643-49-6  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF- $\alpha$ )

IT 167099-00-5P 167099-01-6P 167099-06-1P 167099-13-0P 167099-15-2P  
 167099-16-3P 167099-17-4P 167099-18-5P 167099-19-6P 172679-01-5P  
 188029-39-2P 188029-82-5P 188029-83-6P 188029-97-2P 188029-99-4P  
 188030-09-3P 203643-40-7P 203643-41-8P 203643-47-4P 203724-92-9P  
 203724-93-0P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF- $\alpha$ )

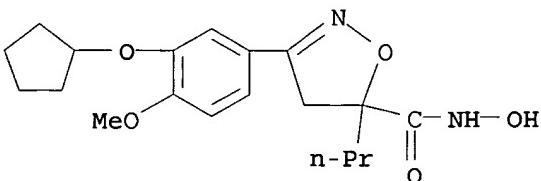
IT 167098-76-2P 167098-85-3P 167098-92-2P  
 167098-93-3P 172678-99-8P 203643-46-3P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and structure activity relations of hydroxamic acid analogs as inhibitors of phosphodiesterase type 4 and TNF- $\alpha$ )

RN 167098-76-2 HCPLUS

CN 5-Isoazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl- (9CI) (CA INDEX NAME)



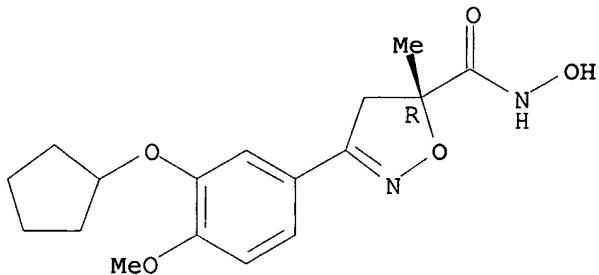
RN 167098-85-3 HCPLUS  
 CN 5-Isoazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-propyl- (9CI) (CA INDEX NAME)



RN 167098-92-2 HCAPLUS

CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5R)- (9CI) (CA INDEX NAME)

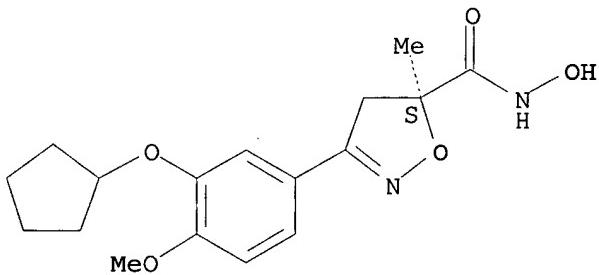
Absolute stereochemistry.



RN 167098-93-3 HCAPLUS

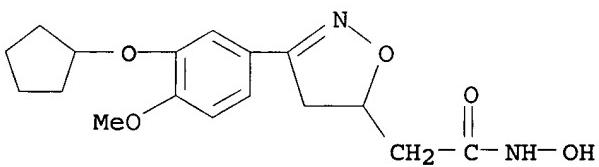
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



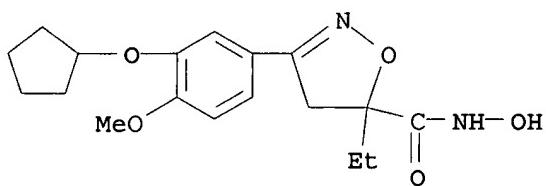
RN 172678-99-8 HCAPLUS

CN 5-Isoxazoleacetamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)



RN 203643-46-3 HCAPLUS

CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-5-ethyl-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)



L7 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 1995:994847 HCAPLUS

DN 124:117297

TI Isoxazoline compounds as inhibitors of TNF release

IN Cohan, Victoria L.; Kleinman, Edward F.

PA Pfizer Inc., USA

SO PCT Int. Appl., 43 pp.

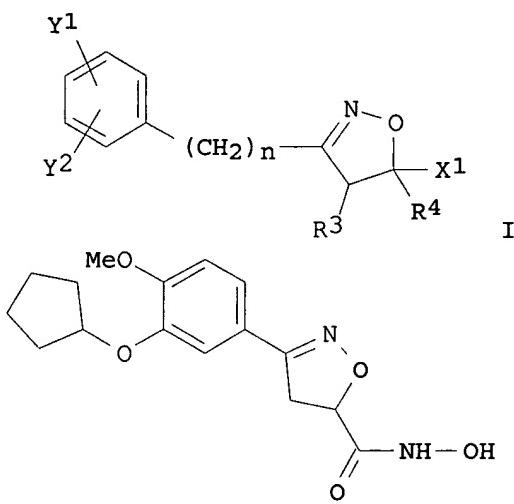
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9524398	A1	19950914	WO 1995-IB78	19950203
	W: AU, CA, CN, FI, JP, KR, MX, NO, NZ, US RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9514647	A1	19950925	AU 1995-14647	19950203
	AU 684887	B2	19980108		
	EP 749428	A1	19961227	EP 1995-906459	19950203
	EP 749428	B1	19980729		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	CN 1143363	A	19970219	CN 1995-192000	19950203
	JP 09505082	T2	19970520	JP 1995-523329	19950203
	AT 169009	E	19980815	AT 1995-906459	19950203
	ES 2118557	T3	19980916	ES 1995-906459	19950203
	CA 2185019	C	20000808	CA 1995-2185019	19950203
	NZ 278667	A	20001222	NZ 1995-278667	19950203
	IL 112847	A1	19991028	IL 1995-112847	19950302
	ZA 9501909	A	19960909	ZA 1995-1909	19950308
	US 5869511	A	19990209	US 1996-700431	19960905
	FI 9603510	A	19960906	FI 1996-3510	19960906
	NO 9603746	A	19961106	NO 1996-3746	19960906
	NO 310496	B1	20010716		
PRAI	US 1994-209125	A	19940309		
	WO 1995-IB78	W	19950203		
OS	MARPAT	124:117297			
GI					



**AB** This invention relates to isoxazoline derivs. I, [X1 = (CH<sub>2</sub>)<sub>q</sub>OH, CH(OH)R<sub>5</sub>, (CH<sub>2</sub>)<sub>m</sub>CONR<sub>6</sub>OH; q, m = 0-5; R<sub>5</sub> = C<sub>1-4</sub> alkyl; R<sub>6</sub> = H, C<sub>1-3</sub> alkyl; n = 0-3; Y<sub>1</sub>, Y<sub>2</sub> = H, C<sub>1-6</sub> alkyl, (un)substituted phenylalkyl or phenoxyalkyl, cycloalkyl, CHF<sub>2</sub>, CF<sub>3</sub>, halo, OR<sub>1</sub>, OR<sub>2</sub>; R<sub>1</sub> = alkyl, phenylalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>, quinolylalkyl; R<sub>2</sub> = alkyl, cycloalkyl, alkoxyalkyl, (un)substituted phenoxyalkyl or phenylalkyl; R<sub>3</sub> = H, alkyl, fluoroalkyl, monohydroxyalkyl, alkoxyalkyl, (un)substituted aminoalkyl, cycloalkyl; R<sub>4</sub> = H, alkyl, fluoroalkyl, monohydroxyalkyl, Ph, alkoxyalkyl, (un)substituted aminoalkyl; or R<sub>3</sub>R<sub>4</sub> forms C<sub>4-7</sub> carbocyclic ring] and their stereoisomeric mixts. or isomers and/or salts, which are inhibitors of tumor necrosis factor (TNF) (no data). I are useful in the treatment or alleviation of inflammatory conditions or diseases, including rheumatoid arthritis, osteoarthritis, asthma, bronchitis, chronic obstructive airway disease, psoriasis, allergic rhinitis, dermatitis, inflammatory bowel disease, sepsis, septic shock, tuberculosis, graft vs. host disease, and cachexia associated with AIDS or cancer. For example, Mitsunobu etherification of isovanillin with cyclopentanol and oximation of the aldehyde function gave 3-cyclopentyloxy-4-methoxybenzaldehyde oxime, which underwent chlorination/dehydrochlorination/1,3-dipolar addition with Et acrylate to form an isoxazoline ring, and finally hydroxamidation with NH<sub>2</sub>OH.HCl and NaOMe, to give title compound II. Preps. of 24 I and approx. 40 intermediates are given.

**IC** ICM C07D261-04

**ICS** A61K031-42; C07D413-12

**CC** 28-6 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

**ST** isoxazoline prepn inhibitor TNF

**IT** Allergy inhibitors

Inflammation inhibitors

Tuberculostatics

(preparation of isoxazolines as TNF release inhibitors)

**IT** Acquired immune deficiency syndrome

Neoplasm  
(treatment of associated cachexia; preparation of isoxazolines as TNF release inhibitors)

**IT** Cachexia

Dermatitis

Hay fever

Psoriasis  
 Sepsis and Septicemia  
     (treatment; preparation of isoxazolines as TNF release inhibitors)  
 IT Inflammation inhibitors  
     (antiarthritics, preparation of isoxazolines as TNF release inhibitors)  
 IT Bronchodilators  
     (antiasthmatics, preparation of isoxazolines as TNF release inhibitors)  
 IT Lung, disease  
     (chronic obstructive, treatment; preparation of isoxazolines as TNF release inhibitors)  
 IT Bronchi  
     (diseases, bronchitis, treatment; preparation of isoxazolines as TNF release inhibitors)  
 IT Transplant and Transplantation  
     (graft-vs.-host reaction, treatment; preparation of isoxazolines as TNF release inhibitors)  
 IT Intestine, disease  
     (inflammatory, treatment; preparation of isoxazolines as TNF release inhibitors)  
 IT Shock  
     (septic, treatment; preparation of isoxazolines as TNF release inhibitors)  
 IT Lymphokines and Cytokines  
     RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)  
         (tumor necrosis factor, preparation of isoxazolines as TNF release inhibitors)  
 IT 699-06-9P, 4-Hydroxybenzaldehyde oxime 3070-65-3P, Ethyl 2-methylenebutyrate 50899-14-4P 51673-94-0P, 3-Hydroxy-4-methoxybenzaldehyde oxime 65818-31-7P 66551-91-5P 94594-91-9P 101074-24-2P 119944-89-7P 158429-65-3P, 4-Methoxy-3-(5-phenylpentyloxy)benzaldehyde 162279-48-3P, 4-Methoxy-3-cyclopentyloxybenzaldehyde oxime 167098-72-8P 167098-94-4P, 4-Methoxy-3-(5-phenylpentyloxy)benzaldehyde oxime 167098-95-5P, 3-Cyclopentyloxybenzaldehyde oxime 167098-96-6P 167098-97-7P 167098-98-8P 167098-99-9P 167099-00-5P 167099-01-6P 167099-02-7P 167099-03-8P 167099-04-9P 167099-05-0P 167099-07-2P 167099-08-3P 167099-09-4P 167099-10-7P 167099-11-8P 167099-12-9P 167099-15-2P 167099-16-3P 167099-17-4P 167099-18-5P 167099-19-6P 167099-20-9P 172679-01-5P 172679-02-6P 172679-03-7P 172679-04-8P 172679-05-9P  
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
         (intermediate; preparation of isoxazolines as TNF release inhibitors)  
 IT 167098-70-6P 167098-73-9P 167098-74-0P 167098-75-1P  
 IT 167098-76-2P 167098-77-3P 167098-78-4P 167098-79-5P  
 IT 167098-81-9P 167098-82-0P 167098-83-1P 167098-84-2P  
 IT 167098-85-3P 167098-86-4P 167098-87-5P  
 IT 167098-88-6P 167098-89-7P 167098-92-2P 167098-93-3P  
 IT 167099-58-3P 167099-60-7P 172678-99-8P 172679-00-4P  
 IT 172779-36-1P  
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
         (preparation of isoxazolines as TNF release inhibitors)  
 IT 50-00-0, Formaldehyde, reactions 74-88-4, Methyl iodide, reactions 96-33-3, Methyl acrylate 96-41-3, Cyclopentanol 97-63-2, Ethyl methacrylate 100-39-0, Benzyl bromide 100-83-4 121-33-5, Vanillin 123-08-0, p-Hydroxybenzaldehyde 140-88-5, Ethyl acrylate 621-59-0, Isovanillin 814-68-6, Acryloyl chloride 932-90-1, Benzaldehyde oxime 4134-14-9, Triethyl 2-phosphonohexanoate 4229-44-1, N-Methylhydroxylamine hydrochloride 4377-41-7, 2-(Chloromethyl)quinoline

5470-11-1, Hydroxylamine hydrochloride 10521-91-2, 5-Phenyl-1-pentanol  
 10544-63-5, Ethyl crotonate 17145-91-4, Triethyl 2-phosphonobutyrate  
 25662-28-6, Methyl 1-cyclopentenoate 31641-78-8, Triethyl  
 phosphonophenylacetate 35051-49-1, Triethyl 2-phosphonopentanoate  
 39161-19-8, 3-Penten-1-ol 94594-90-8 108448-77-7, (+)-L-2,10-Camphor  
 sultam 172679-06-0 172679-07-1

RL: RCT (Reactant); RACT (Reactant or reagent)

(starting material; preparation of isoxazolines as TNF release inhibitors)

IT

167098-70-6P 167098-75-1P 167098-76-2P

167098-85-3P 167098-86-4P 167098-87-5P

167098-92-2P 167098-93-3P 172678-99-8P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

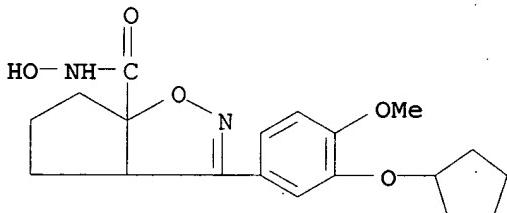
(preparation of isoxazolines as TNF release inhibitors)

RN

167098-70-6 HCPLUS

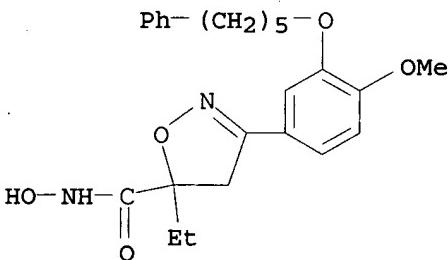
CN

6aH-Cyclopent[d]isoxazole-6a-carboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-3a,4,5,6-tetrahydro-N-hydroxy- (9CI) (CA INDEX NAME)



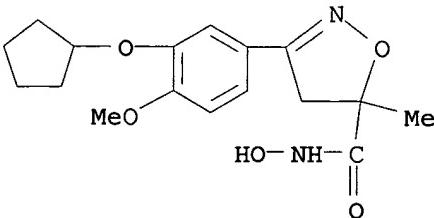
RN 167098-75-1 HCPLUS

CN 5-Isoxazolecarboxamide, 5-ethyl-4,5-dihydro-N-hydroxy-3-[4-methoxy-3-[(5-phenylpentyl)oxy]phenyl]- (9CI) (CA INDEX NAME)



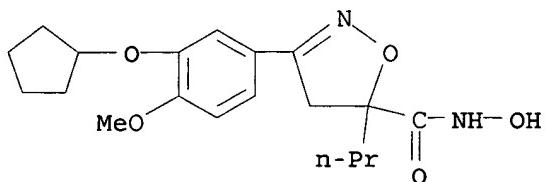
RN 167098-76-2 HCPLUS

CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl- (9CI) (CA INDEX NAME)



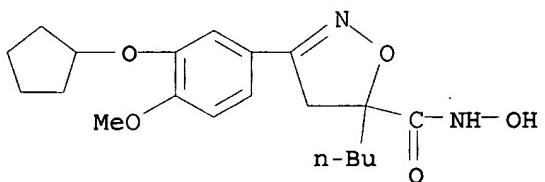
RN 167098-85-3 HCAPLUS

CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-propyl- (9CI) (CA INDEX NAME)



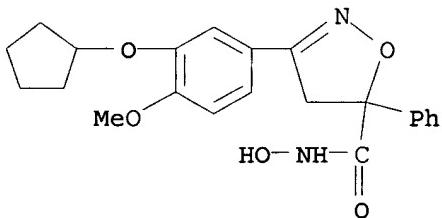
RN 167098-86-4 HCAPLUS

CN 5-Isoxazolecarboxamide, 5-butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)



RN 167098-87-5 HCAPLUS

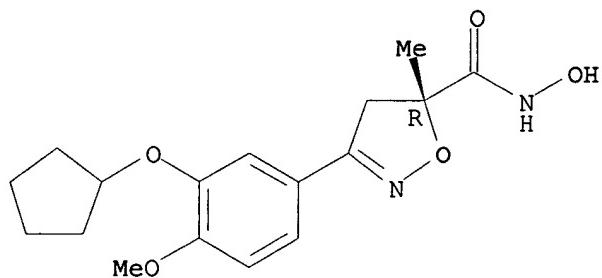
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-phenyl- (9CI) (CA INDEX NAME)



RN 167098-92-2 HCAPLUS

CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5R)- (9CI) (CA INDEX NAME)

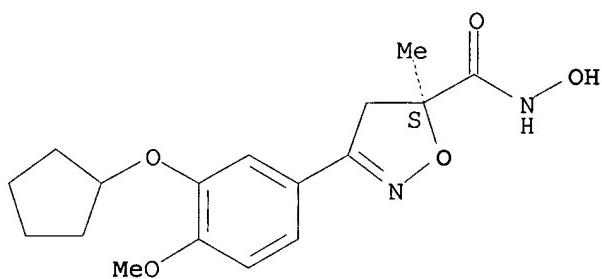
Absolute stereochemistry.



RN 167098-93-3 HCAPLUS

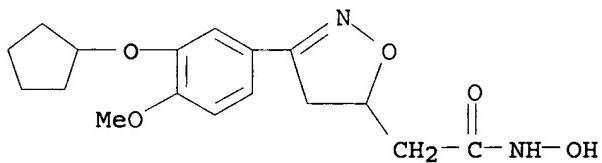
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 172678-99-8 HCAPLUS

CN 5-Isoxazoleacetamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)



L7 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 1995:763861 HCAPLUS

DN 123:169610

TI Isoxazoline compounds as antiinflammatory agents

IN Kleinman, Edward F.

PA Pfizer Inc., USA

SO PCT Int. Appl., 36 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

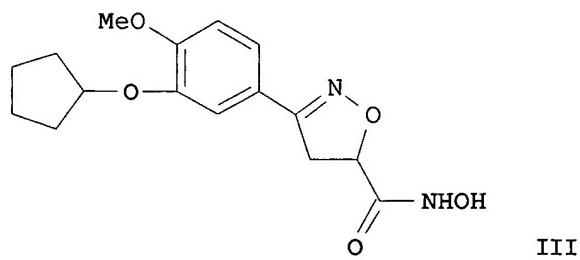
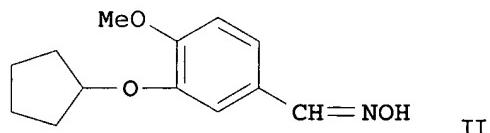
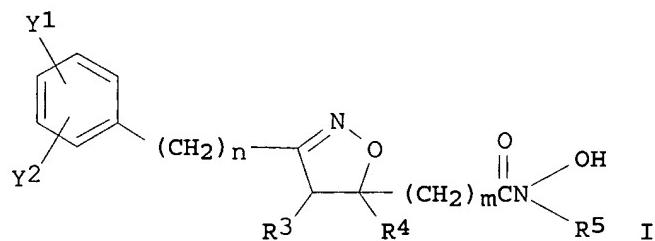
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9514681	A1	19950601	WO 1994-IB333	19941026
	W: AU, BR, CA, CN, CZ, HU, JP, KR, NO, NZ, PL, RU, US, US				

RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE  
 CA 2176255 AA 19950601 CA 1994-2176255 19941026  
 CA 2176255 C 19990223  
 AU 9478218 A1 19950613 AU 1994-78218 19941026  
 AU 687452 B2 19980226  
 EP 730588 A1 19960911 EP 1994-929001 19941026  
 EP 730588 B1 19970702

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE  
 CN 1136314 A 19961120 CN 1994-194274 19941026  
 CN 1046274 B 19991110  
 JP 09500147 T2 19970107 JP 1994-514933 19941026  
 BR 9408174 A 19970527 BR 1994-8174 19941026  
 AT 154932 E 19970715 AT 1994-929001 19941026  
 ES 2104424 T3 19971001 ES 1994-929001 19941026  
 HU 76784 A2 19971128 HU 1996-1412 19941026  
 CZ 283564 B6 19980513 CZ 1996-1510 19941026  
 IL 111670 A1 19980816 IL 1994-111670 19941117  
 FI 9405557 A 19950527 FI 1994-5557 19941125  
 ZA 9409379 A 19960527 ZA 1994-9379 19941125  
 US 5716967 A 19980210 US 1996-640944 19960515  
 NO 9602127 A 19960524 NO 1996-2127 19960524

PRAI US 1993-157248 A2 19931126  
 US 1994-262086 A2 19940617  
 WO 1994-IB333 W 19941026

OS CASREACT 123:169610; MARPAT 123:169610  
 GI



AB The invention relates to new isoxazolines I [m, n = 0-3; Y1, Y2 = H, alkyl, (un)substituted phenylalkyl or phenoxyalkyl, cycloalkyl, CHF<sub>2</sub>, CF<sub>3</sub>,

halo, OR<sub>1</sub>, OR<sub>2</sub>; R<sub>1</sub> = alkyl, phenylalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub>; R<sub>2</sub> = alkyl, cycloalkyl, alkoxyalkyl, (un)substituted phenoxyalkyl, phenylalkyl, or indanylalkyl, bicycloalkyl; R<sub>3</sub> = H, alkyl, fluoroalkyl, hydroxyalkyl, alkoxyalkyl; R<sub>4</sub> = H, alkyl, fluoroalkyl, hydroxyalkyl, Ph, alkoxyalkyl, (di)(alkyl)aminoalkyl, alkanoylaminooalkyl, cycloalkyl; or R<sub>3</sub>R<sub>4</sub> form carbocyclic ring of 4-7 atoms; R<sub>5</sub> = H, alkyl]. I are selective inhibitors of phosphodiesterase type IV (no data), and are useful in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, etc. For example, etherification of isovanillin with cyclopentanol by the Mitsunobu method, and oximation of the resultant aldehyde-ether, gave oxime II. Reaction of II with N-chlorosuccinimide and pyridine, followed by cyclization of the product with Et acrylate in the presence of Et<sub>3</sub>N in situ, and reaction of the Et ester product with NH<sub>2</sub>OH.HCl and NaOMe in MeOH, gave title compound III. Preps. of approx. 20 I and 40 precursors are described.

IC ICM C07D261-04

ICS A61K031-42

CC 28-6 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

ST isoxazoline hydroxamic acid prepn antiinflammatory; phosphodiesterase inhibitor isoxazoline hydroxamic acid prepn; PDE IV inhibitor isoxazoline hydroxamic acid

IT Allergy inhibitors

Inflammation inhibitors

(preparation of isoxazolines as PDE type IV inhibitors)

IT Acquired immune deficiency syndrome

Dermatitis

Psoriasis

Shock

(treatment; preparation of isoxazolines as PDE type IV inhibitors)

IT Inflammation inhibitors

(antiarthritics, preparation of isoxazolines as PDE type IV inhibitors)

IT Bronchodilators

(antiasthmatics, preparation of isoxazolines as PDE type IV inhibitors)

IT Lung, disease

(chronic obstructive, treatment; preparation of isoxazolines as PDE type IV inhibitors)

IT Bronchi

(diseases, bronchitis, treatment; preparation of isoxazolines as PDE type IV inhibitors)

IT 699-06-9P, 4-Hydroxybenzaldehyde oxime 3070-65-3P, Ethyl 2-methylenebutyrate 3550-06-9P, Ethyl 2-propylacrylate 3618-37-9P, Ethyl 2-butylacrylate 22286-82-4P, Ethyl 2-phenylacrylate 50899-14-4P, 3-Phenyl-2-isoxazoline-5-carboxylic acid ethyl ester 51673-94-0P, 3-Hydroxy-4-methoxybenzaldehyde oxime 119944-89-7P 158429-65-3P, 4-Methoxy-3-(5-phenylpentyloxy)benzaldehyde 162279-48-3P, 3-(Cyclopentyloxy)-4-methoxybenzaldehyde oxime 167098-71-7P

167098-72-8P 167098-94-4P, 4-Methoxy-3-(5-phenylpentyloxy)benzaldehyde oxime 167098-95-5P, 3-(Cyclopentyloxy)benzaldehyde oxime 167098-96-6P, 4-(Cyclopentyloxy)-3-methoxybenzaldehyde oxime 167098-97-7P

167098-98-8P 167098-99-9P 167099-00-5P 167099-01-6P 167099-02-7P

167099-03-8P 167099-04-9P 167099-05-0P 167099-06-1P 167099-07-2P

167099-08-3P 167099-09-4P, 3-(3,4-Dimethoxyphenyl)-2-isoxazoline-5-carboxylic acid methyl ester 167099-10-7P 167099-11-8P 167099-12-9P

167099-13-0P 167099-15-2P 167099-16-3P 167099-17-4P 167099-18-5P

167099-19-6P 167099-20-9P 167099-21-0P 172679-04-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of isoxazolines as PDE type IV inhibitors)

IT 167098-70-6P 167098-73-9P 167098-74-0P 167098-75-1P

167098-76-2P 167098-77-3P 167098-78-4P 167098-79-5P  
 167098-80-8P 167098-81-9P 167098-82-0P 167098-83-1P 167098-84-2P,  
 3-Phenyl-2-isoxazoline-5-hydroxamic acid 167098-85-3P  
 167098-86-4P 167098-87-5P 167098-88-6P 167098-89-7P  
 167098-92-2P 167098-93-3P 172678-99-8P  
 172679-00-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of isoxazolines as PDE type IV inhibitors)

IT 9025-82-5, Phosphodiesterase

RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)

(preparation of isoxazolines as PDE type IV inhibitors)

IT 50-00-0, Formaldehyde, reactions 74-88-4, Methyl iodide, reactions 96-33-3, Methyl acrylate 96-41-3, Cyclopentanol 97-63-2, Ethyl methacrylate 100-39-0, Benzyl bromide 100-83-4 121-33-5, Vanillin 123-08-0, p-Hydroxybenzaldehyde 140-88-5, Ethyl acrylate 621-59-0, Isovanillin 627-27-0, 3-Buten-1-ol 814-68-6, Acryloyl chloride 932-90-1, Benzaldehyde oxime 2627-86-3, (S)-(-)- $\alpha$ -Methylbenzylamine 4134-14-9, Triethyl 2-phosphonohexanoate 4229-44-1, N-Methylhydroxylamine hydrochloride 4377-41-7, 2-(Chloromethyl)quinoline 5470-11-1, Hydroxylamine hydrochloride 10521-91-2, 5-Phenyl-1-pentanol 10544-63-5, Ethyl crotonate 17145-91-4, Triethyl 2-phosphonobutyrate 25662-28-6, Methyl 1-cyclopentenoate 31641-78-8, Triethyl phosphonophenylacetate 35051-49-1, Triethyl 2-phosphonopentanoate 94594-91-9 108448-77-7, (+)-L-2,10-Camphorsultam

RL: RCT (Reactant); RACT (Reactant or reagent)

(starting material; preparation of isoxazolines as PDE type IV inhibitors)

IT 167098-70-6P 167098-75-1P 167098-76-2P

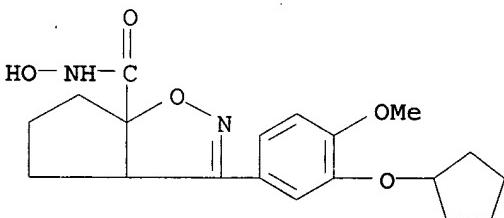
167098-85-3P 167098-86-4P 167098-87-5P

167098-92-2P 167098-93-3P 172678-99-8P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of isoxazolines as PDE type IV inhibitors)

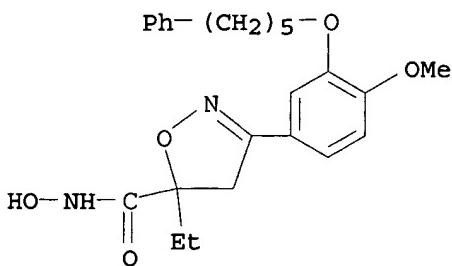
RN 167098-70-6 HCPLUS

CN 6aH-Cyclopent[d]isoxazole-6a-carboxamide, 3-[3-[(cyclopentyloxy)-4-methoxyphenyl]-3a,4,5,6-tetrahydro-N-hydroxy- (9CI) (CA INDEX NAME)

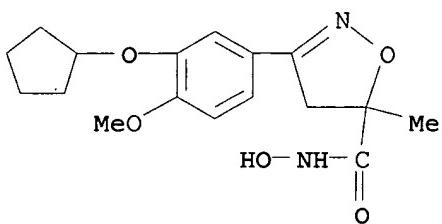


RN 167098-75-1 HCPLUS

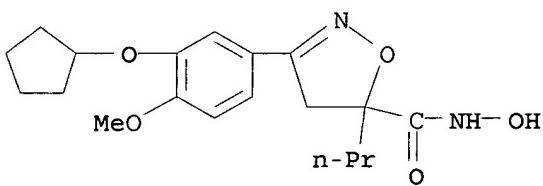
CN 5-Isoxazolecarboxamide, 5-ethyl-4,5-dihydro-N-hydroxy-3-[4-methoxy-3-[(5-phenylpentyl)oxy]phenyl]- (9CI) (CA INDEX NAME)



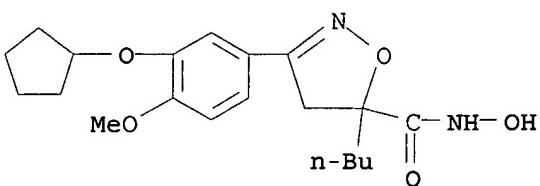
RN 167098-76-2 HCAPLUS  
 CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl- (9CI) (CA INDEX NAME)



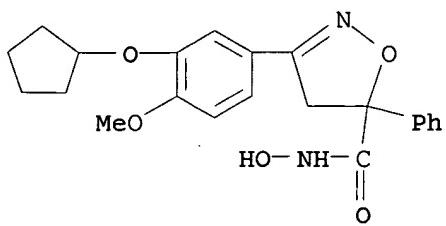
RN 167098-85-3 HCAPLUS  
 CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-propyl- (9CI) (CA INDEX NAME)



RN 167098-86-4 HCAPLUS  
 CN 5-Isoxazolecarboxamide, 5-butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)



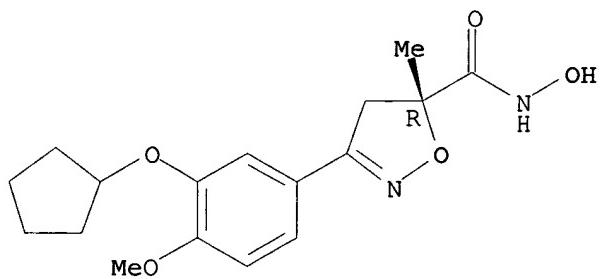
RN 167098-87-5 HCAPLUS  
 CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-phenyl- (9CI) (CA INDEX NAME)



RN 167098-92-2 HCAPLUS

CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5R)- (9CI) (CA INDEX NAME)

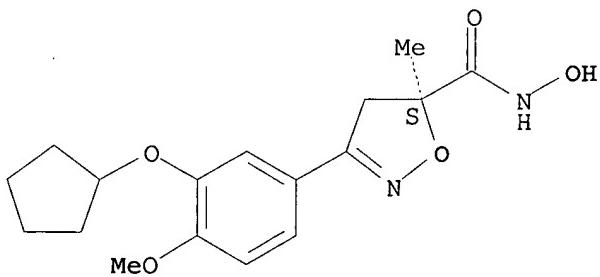
Absolute stereochemistry.



RN 167098-93-3 HCAPLUS

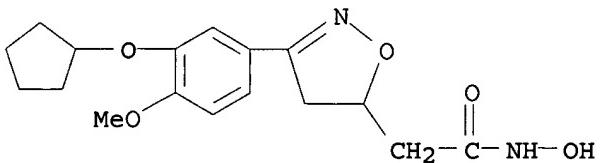
CN 5-Isoxazolecarboxamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy-5-methyl-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 172678-99-8 HCAPLUS

CN 5-Isoxazoleacetamide, 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5-dihydro-N-hydroxy- (9CI) (CA INDEX NAME)



SACKEY 10/697545 02/10/2006

Page 58

=>

KATHLEEN FULLER EIC1700 REMSEN 4B28 571/272-2505